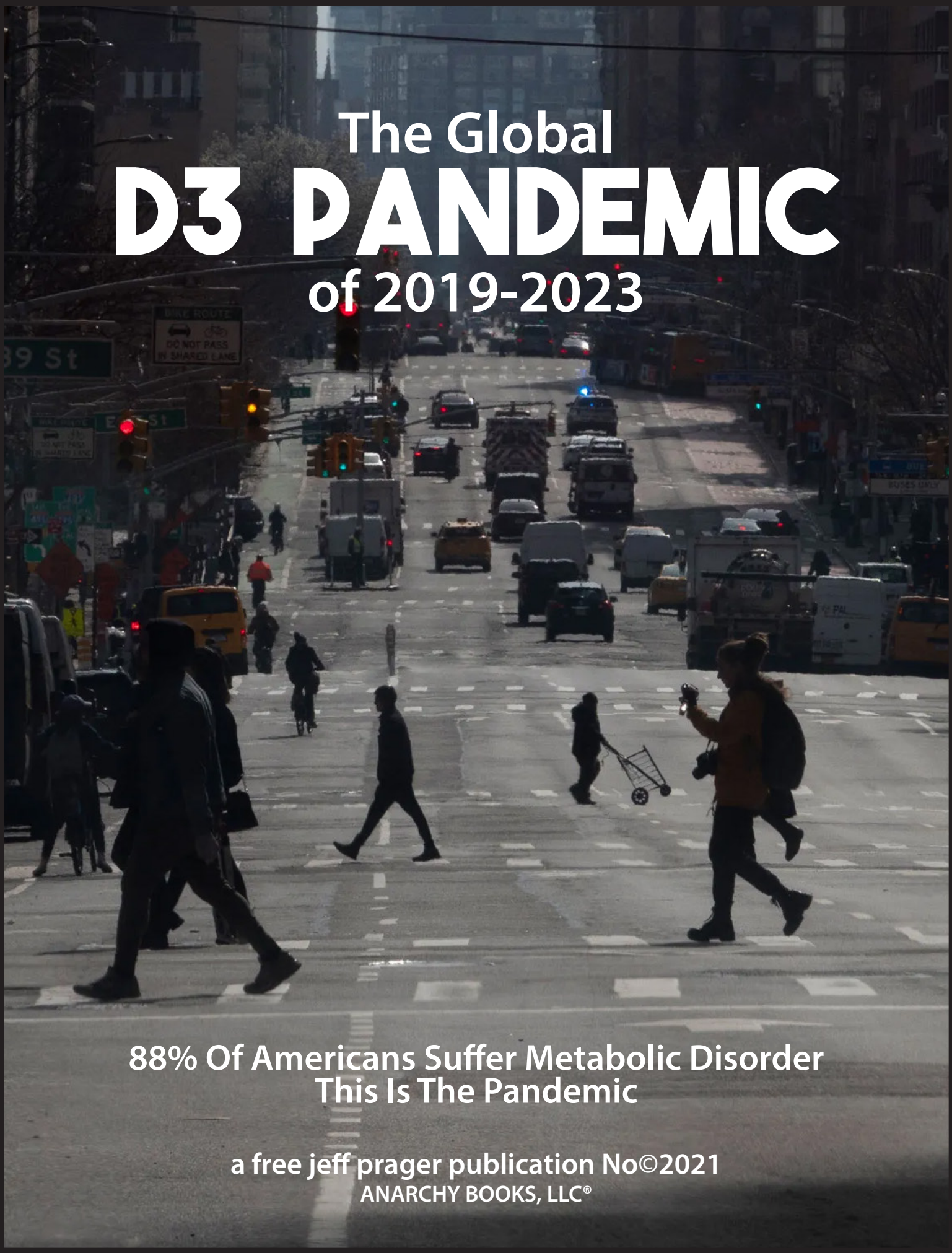

The Global D3 PANDEMIC of 2019-2023

88% Of Americans Suffer Metabolic Disorder
This Is The Pandemic

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INTRODUCTION

The COVID jab reprograms your innate and adaptive immune systems, causing immune depletion.

Repeated boosters cause what's called "immune exhaustion," wherein you essentially have no immune system.

Data also show that the more heavily "vaccinated" a population is, the higher the case rate gets.

UK Yellow Card data (week 46) show that hospitaliztions and deaths are in the fully vaccinated, over 80%.

As predicted, we are rapidly approaching a time when the unvaccinated might be imprisoned for no other reason than their refusal of an experimental gene transfer injection.

In early January 2021, a New York bill (A416) was introduced that would give the governor and his or her delegates the power to remove and/or indefinitely detain anyone suspected of being a threat to public health. Detainees would be kept in a "medical facility or other appropriate facility" — in other words, a medical prison camp — for a maximum of 60 days, although a court could extend the detention in 90-day increments, indefinitely.

In Australia, medical incarceration is already underway. Anyone who has come in close contact with someone who tests positive must spend 14 days in the quarantine camp, even if they are triple jabbed and test negative for COVID.

In Austria vaccination is mandatory for the entire population.

MASS MURDER BY THE MEDICAL PROFESSION (Family Doctors) THROUGH THERAPEUTIC NIHILISM — REFUSING TO SEE OR TREAT COVID PATIENTS —

by Jeff Prager • December 31, 2021

If you or I had Herpes, Influenza, Syphilis, Gonorrhea, Adenovirus, Cancer, Scabies, Head Lice, the common cold, an eye infection, Diabetes, Lupus, Pneumonia or any of 100s of disorders, our family physician would have scheduled an appointment and seen and treated us. Not so with COVID.

I remember almost 2 years ago, just before COVID was recognized and known, my family physicians excitement that he was chosen to set up the Telemedicine Program at his clinic, the clinic I used to go to. With COVID we were ALL told to stay home and isolate, take Tylenol (not indicated for COVID) and if we have trouble breathing, go to the hospital. It didn't dawn on me at the time that the Telemedicine protocol was designed to refuse to see COVID patients and allow them to self-isolate with Tylenol while the virus replicated exponetially, making us too sick to survive by the time we arrived at the hospital.

Who Overflowed The Hospitals?

Failure to treat early and staying home for a week or so allowed the virus to replicate. WE overflowed the hospitals because the CDC protocol was "there is no treatment for COVID" and without early treatment we got sick and in fact with the virus replicating like mad while we were isolating at home, most of us were unrecoverable once reaching the hospital. The virus had replicated and the harms as a result were too far along to save us. We were given Remdisivir and a ventilator, no family members were allowed into the COVID wards and our loved ones died alone.

The Death Protocol

Dr's Zelenco, McCullough, Kory (FLCCC), Gold (AFLDS), Cole, Bhakdi, Montagnier (Nobel Prize for discovering HIV), Malone and especially Dr. David Martin were not silenced nor did they fear treating patients. Collectively, their treatments would have saved 85-90% of those that died.

The CDC Protocol is Remdisivir and the Ventilator. 85% of patients on ventilators died. Remdisivir causes liver failure and allows fluid to collect in the body meaning your lungs fill with fluid as well. This is a Protocol by the Centers For Disease Control results in mass death. Your government wants you dead.

Had we been treated early with Ivermectin, which Ann and I take by prescription (13.5mg twice a week) and Zinc, Magnesium, Liposomal D3, K2, Melatonin, Food Grade NAC, Food Grade Ascorbic Acid (Vitamin C), the B complex, Vitamin A, Quercetin and ECGC we would have survived.

Going After The Kids. WHY?

The answer is simple. If enough children are injected the pharmaceutical companies can get the injection onto the childhood vaccine schedule. That's the goal behind vaccinating children who have an almost 100% survival rate from COVID, if they get sick at all.

Spreading The Disease

The peer review uses two terms to describe vaccines. A 'Sterile Vaccine" and a "Leaky Vaccine". The COVID injection is a Leaky Injection meaning it does not prevent getting COVID and it does not prevent transmission of

COVID to others. This means there are over 200,000 injected Americans walking around with higher viral titers than those who are unvaccinated with COVID and they are spreading the virus to all they come in contact with. Now COVID cannot be contracted by touching surfaces and it can only be contracted in poorly ventilated areas and one must spend a significant period of time in such places. In general, it takes almost 3 hours to acquire COVID under such circumstances. So COVID is not easily transmissable.

I Can't Get COVID

If you have a D3 level above 50 you CAN NOT acquire a virus. This includes COVID, Influenza, Adenovirus, the 4 Corona viruses that cause the common cold, Respiratory Syncytial Virus, Parainfluenza 1, 2, 3 or 4 and many other viruses that circulate during the North American viral season (usually November through April). My D3 level tested less than 3 weeks ago is 64 nanogram's per milliliter and Ann's is 80.1 nanogram's per milliliter. We cannot contract a virus of any kind. This is a simple medical fact. Dr. Fauci (excuse me, I jusat spit up in my mouth mentioning his name) stated in an interview at a small Kansas television station that he takes 8-9000 International Units (IU's) of vitamin D3 daily.

Why he didn't issue a regular Public Service Announcement (PSA) for Americans to begin supplementing with high daily doses of D3, K2 and Magnesium is a question I can't answer. But had he done so 10s of 1000s of lives would have been saved.

Death Comes With Many Faces

These modified mRNA injections that cause your body to manufacture the Spike Protein, which is toxic to the human body, will cause death and disorder for years to come. In particular, Parkinson's Disease, Muscular Dystrophy, Neurological disorders and worst of all, one of almost 100 Autoimmune disorders.

The Peer Review

I included peer review in this volume on Vitamin D3 and Vitamin C, both old and new peer review, so that the reader can see that we already knew years ago and we know now that high doses of D3 and Vitamin C literally clear COVID and create miraculous recoveries. Add Ivermectin at double the normal dosage for a week and no one needed to die. The CDC Protocol—do not treat allowing viral replication—was designed to murder us and once in the hospital the treatment protocol of Remdisivir and Ventilators assured our death.

Yes, They Want You Dead
Depopulation IS The Silent, Secret Agenda

According to Dr. Mike Yeadon, a Pfizer VP in charge of Respiratory disease investigation and a pro-vaccine medical professional who spent his life researching and developing vaccines stated that for every 100 children injected 99 will eventually die. Dr. Judy Mikovitz, a microbiologist from Fort Detricks level 4 Biolab stated over the next 3-10 years 50 million Americans will die from the gene therapy injection. Dr. Helen Cahill, another microbiologist from the UK stated the same. Dr. Bryan Ardis and Dr. Yeadon in his video "Warning To The World, both stated that these gene therapy injections are a Eugenics program. Even Dr. Luc Montagnier has stated the same and at 83-years-old he came out of retirement, reopened his lab and is performing the Pathology on only deceased, injected patients to determine what killed them. He's finding Spike Proteins throughout the human body destroying tissue throughout the body. We're Guinea Pigs in a deadly experiment notwithstanding NO corona virus vaccine has ever worked. Every attempt over the last 20 years to develop a corona virus vaccine has had the same results, whether with ferrets, rats, mice or primates, when exposed to the wild virus months later most of the animals died. Think that over.

88% of Americans suffer metabolic disorder, the precursor to all diseases known to humanity. Metabolic disorder means you're on your way to illness, disease and disorder. This means that just 12% of us or 39 million out of 329.5 billion are metabolically healthy and that's a shameful statistic to have to type. Had the US government put out a regular, daily Public Service Announcement (PSA) that all Americans needed to have their D3 levels checked and supplement to 40-60 nanogram's per milliliter using Liposomal D3 with K2 and Magnesium and had we been instructed through additional PSA's that we should be using Quercetin and Zinc daily, we may have saved 100s of 1000s of lives. A multivitamin and other vitamins and neutraceuticals help as well.

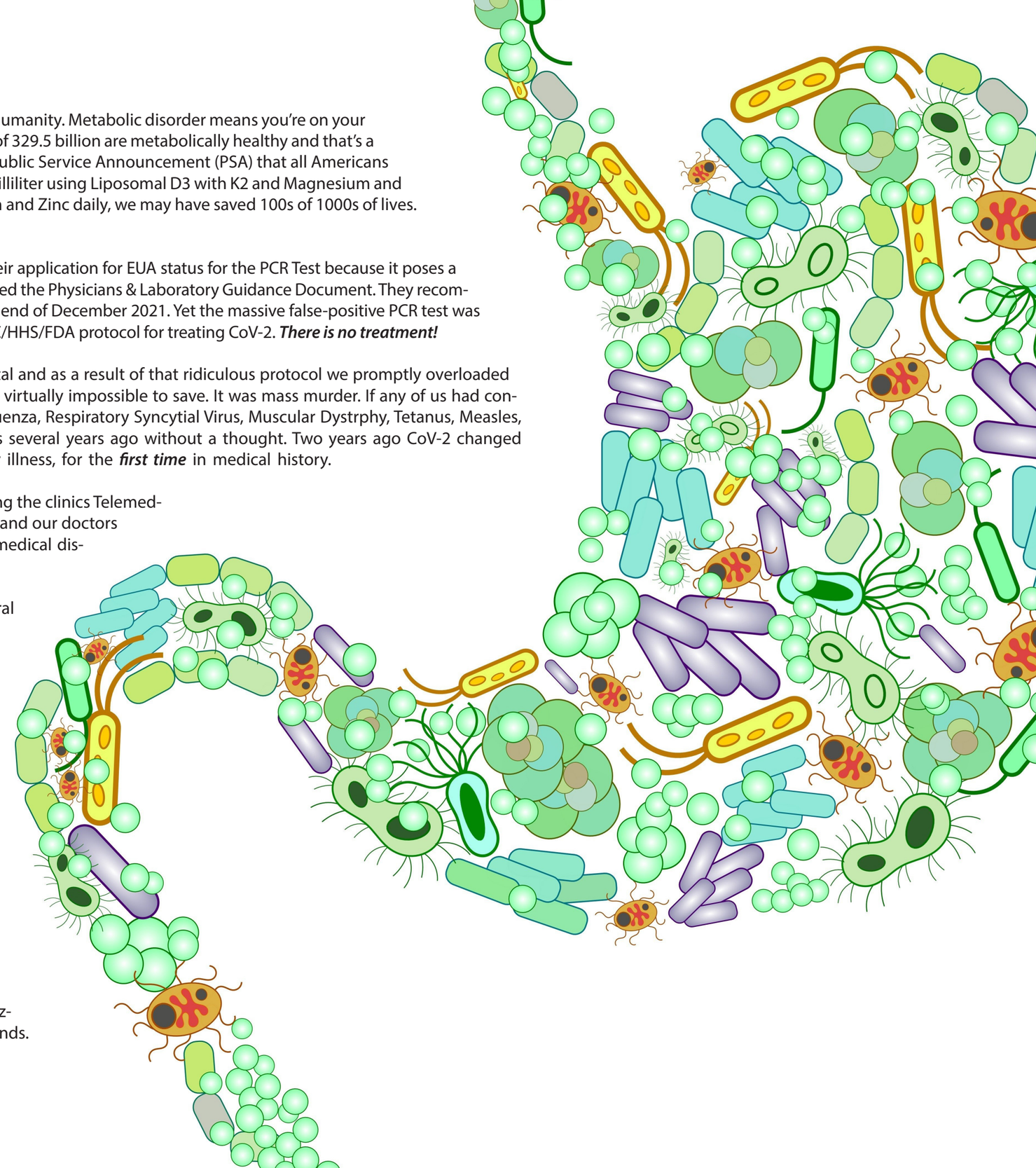
The CDC declared, months ago in a Guidance Document that they were recalling their application for EUA status for the PCR Test because it poses a "danger" (their word) to those that use it. I wrote about it months ago when they posted the Physicians & Laboratory Guidance Document. They recommended other FDA approved tests and have banned the PCR Test from use as of the end of December 2021. Yet the massive false-positive PCR test was and is still being used to increase "cases," and instill massive fear. Worse yet is the CDC/HHS/FDA protocol for treating CoV-2. ***There is no treatment!***

Stay home, take Tylenol and when and if you're unable to breathe go to the hospital and as a result of that ridiculous protocol we promptly overloaded the hospitals with patients whose viral load had replicated for days and who were virtually impossible to save. It was mass murder. If any of us had contracted Herpes, Syphillus, Ghonnorea, Hepatitus, Warts, Cancer, Influenza, Parainfluenza, Respiratory Syncytial Virus, Muscular Dystrphy, Tetanus, Measles, Mumps or Chicken Pox our family physicians would have seen us and treated us several years ago without a thought. Two years ago CoV-2 changed US Medical Procedure. No treatment for a respiratory illness, for ANY respiratory illness, for the ***first time*** in medical history.

I remember clearly when my family physician told me he was tasked with developing the clinics Telemedicine Platform. He was excited and I didn't think much of it until CoV-2 came along and our doctors began appearing on our phones and computers in Zoom meetings. A complete medical disconnect accepted by most.

We, our family physicians actually, overloaded the hospitals with patients whose viral load was replicating for days at home and who, by the time they reached the hospital, had little chance of survival. Ivermectin, Hydroxychloroquine—I'm not going to belabor the villifying propoganda—and D3, infusions of vitamin C, antibiotics, anticoapgulants and anti-inflammatories, corticosteroids, inhaled Budesinide, Peroxide, Lugols, etc., all as early treatment make CoV-2 an easily treatable respiratory infection and not the Pandemic it's alleged to be. The numbers had to be faked to reach the ridiulous conclusions that an injection would save the day. Four boosters later ... No one needed to die. Zelenko, McCullough and Kory are just a few of the names that will be remembered, historically, as heroes, as having moral and ethical courageous when the vast majority of doctors not only failed their patients, they failed their most sacred oath — to do no harm. They committed murder by therapeutic nihilism.

This was a relatively normal influenza-like illness—when treated early no one needed to be hospitalized—that was allowed to replicate in the population while isolated at home and then being fought with a one-size-fits-all experimental genetic injection based on SARS CoV-1 (CoV-2 has not been isolated) and a computer simulation of Alpha (not isolated) when computer simulations of Delta and Omicron are alleged to be present (both as yet to be isolated) using a non-sterilizing injection that allows transmission and infection. Someone just plain lost their minds.



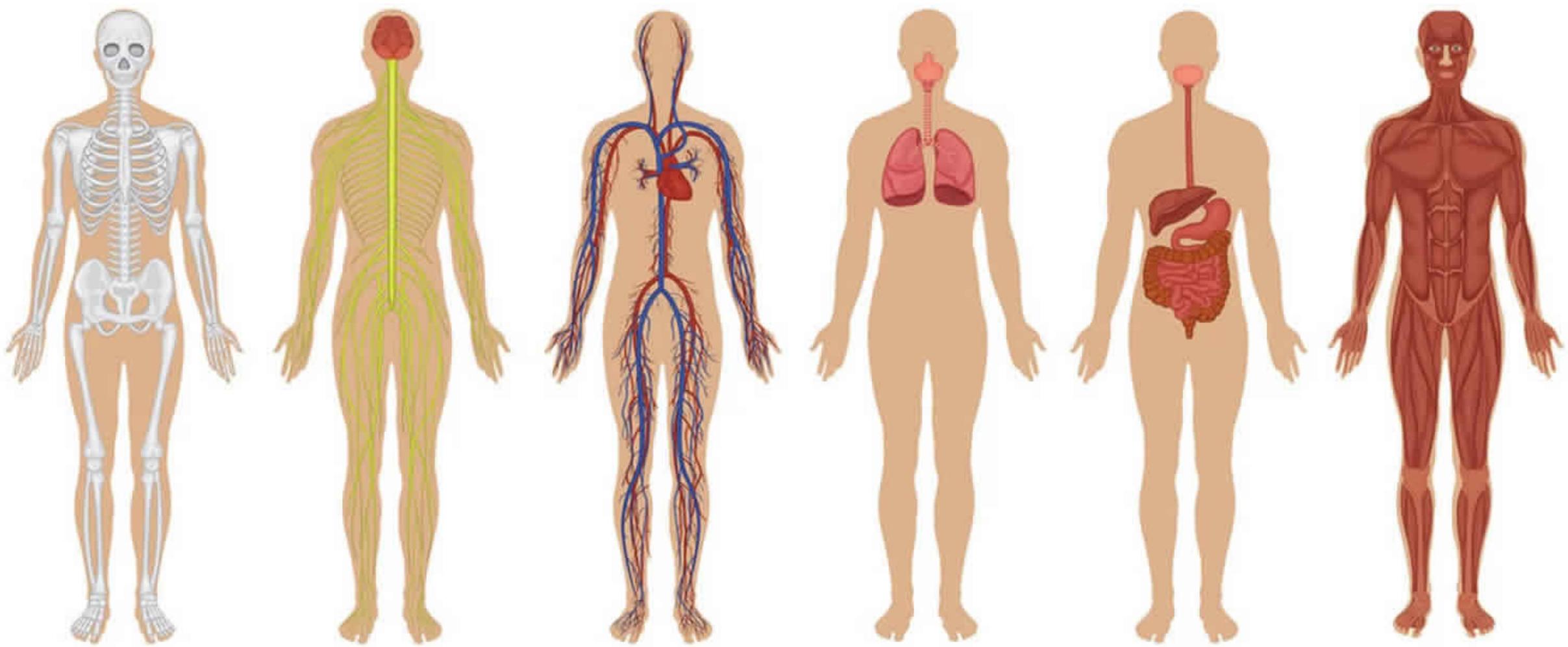
In fact, there's been a collective loss of critical thinking in our anxiety-ridden states of mind referred to by psychologists and psychiatrists as mass formation as written about extensively by Prof. Dr. Mattias Desmet. Similar to mass psychosis.

Hard to believe, right? According to both Dr's Peter McCullough and Vladimir Zelenko the vast majority of 815,000 US Covid-19 deaths could have been prevented (85% or more) with any of several early-treatment protocols. Instead, we engaged in Euthanisia at best and a murderous Genocide at worst. The peer review in this volume is older, so that you'll understand we've always known. We've known that D3 fights almost every disease known, that almost every cell has receptors for vitamin D and Dr. Fauci himself stated he takes 8,000-9,000 I.U.'s of vitamin D3 per day during a TV interview—no mention of K2 and magnesium, necessary to metabolize D3 properly for maximum benefit. In fact the video played once or twice on an obscure southern TV station but the major media never picked it up.

Our governments want us to be sick, vulnerable, immune compromised, and we don't have to be. After years of breathing toxic air, being injected with autoimmune causing vaccine adjuvants, breathing noxious pesticides, eating petroleum-based artificial colorings and sweeteners consuming bisphenol analogues, breathing and eating glyphosate, drinking toxic water and eating toxic food we've been biologically primed for disease and a single bad respiratory illness season or two is enough to throw us into metabolic Armageddon—WITHOUT early treatment. Yet we Early Treatment we all survive.

This book is a brief examination of the peer review on vitamins and minerals, often older peer review so we can see that the knowledge is known and established and the peer review on Ivermectin. Hydroxychloroquine has a larger cache of peer review, has been around 30 years longer and has an equally successful effect at both preventing as a prophylactic and treating CoV-2 out-patient and in-hospital. I chose Ivermectin because that's what I use and I've had great success in regards to obtaining it and tolerating it. It's virtually a "nothing pill" and one wouldn't know one had taken it. At lease that's been my experience.

The peer review contained in this volume proves we can effectively treat CoV-2, that these highly effective treatments are being suppressed and that the death spiral has been therapeutic nihilism at best or a complete medical blunder causing mass murder at worst. Then again, in my opinion, it was planned for decades and Event 201 and other very similar dress rehearsals prior to it combined with the damning patent information revealed by Dr. David Martin and Robert F. Kennedy, Jr's expose on Tony Fauci make this monumentally clear. Planned from the very beginning. A bioweapons attack on the entire human race. It's almost too far fetched to believe but based on the GZM, it instantly becomes all the more believable.



UNC GILLINGS SCHOOL OF GLOBAL PUBLIC HEALTH

Only 12 percent of American adults are metabolically healthy

https://www.sciencedaily.com/releases/2018/11/181128115045.htm

November 28, 2018

The prevalence of optimal metabolic health in American adults is 'alarmingly low,' even among people who are normal weight, a new study finds.

According to researchers at the University of North Carolina at Chapel Hill's Gillings School of Global Public Health, only 1 in 8 Americans is achieving optimal metabolic health, which carries serious implications for public health. Poor metabolic health leaves people more vulnerable to developing Type 2 diabetes, cardiovascular disease and other serious health issues.

The study presents the most updated United States data on metabolic health, which is defined here as having optimal levels of five factors: (1) blood glucose, (2) triglycerides, (3) high-density lipoprotein (HDL) cholesterol, (4) blood pressure and (5) waist circumference, without the need for medications.

For the study, researchers examined National Health and Nutrition Examination Survey (NHANES) data from 8,721 people in the U.S. between 2009 and 2016 to determine how many adults are at low versus high risk for chronic disease. Data revealed that only 12.2 percent of American adults are metabolically healthy, which means that only 27.3 million adults are meeting recommended targets for cardiovascular risk factors management, according to researchers.

In the last decade, the thresholds for common health measures – for example, those used to determine whether someone has high blood pressure or blood sugar (glucose) levels – have been lowered by respected professional medical societies. Researchers say these more restrictive guidelines may mean that a smaller proportion of people are meeting the optimal levels for the cardiovascular risk factors.

"The study fills a gap," said Joana Araujo, PhD, postdoctoral research associate in nutrition and the study's first author. "We wanted to know how many American adults really meet the guidelines for all of these risk factors and are within optimal levels for disease prevention and health. Based on the data, few Americans are achieving metabolic health, which is quite alarming and should spur renewed attention to population-based interventions."

The data showed that being more physically active, female, younger, more educated and a nonsmoker were factors associated with being more metabolically healthy. Being non-Hispanic black or having a higher body mass index (BMI) meant people were less likely to be metabolically healthy.

"We also looked at how health-related behaviors might play into metabolic health – and how the proportion

of people who are metabolically healthy changes when BMI, physical activity or smoking are higher or lower," Araujo said. "For example, less than 1 percent of obese adults are metabolically healthy. On the other hand, people who exercise more appear to have higher levels of metabolic health."

The authors call for further study to understand the mechanisms of risk factor development, with a focus on people of normal weight as well as heavier adults.

"Most disturbing is the absence of optimal metabolic health in adults who had obesity, less than a high school education, were not physically active and were current smokers.[…] Stronger and more widely accessible strategies to promote healthier lifestyles are urgently warranted," wrote Araujo and colleagues.

The study, "Prevalence of Optimal Metabolic Health in American Adults: National Health and Nutrition Examination Survey 2009-2016," was published online Nov. 28 in the journal Metabolic Syndrome and Related Disorders.

Co-authors are Jianwen Cai, PhD, Cary C. Boshamer Distinguished Professor and vice chair of biostatistics, and senior author June Stevens, PhD, American Institute for Cancer Research/World Cancer Research Fund Distinguished Professor of nutrition and epidemiology.

Metabolic Syndrome and Related Disorders • Vol. 17, No. 1 Original Article • Free Access

Prevalence of Optimal Metabolic Health in American Adults: National Health and Nutrition Examination Survey 2009–2016

By Joana Araújo, Jianwen Cai, and June Stevens

Published Online: February 8th, 2019
https://doi.org/10.1089/met.2018.0105

Background: Several guidelines for cardiometabolic risk factor identification and management have been released in recent years, but there are no estimates of current prevalence of metabolic health among adults in the United States. We estimated the proportion of American adults with optimal cardiometabolic health, using different guidelines.

Methods: Data from the National Health and Nutrition Examination Survey 2009–2016 were analyzed (n = 8721). Using the most recent guidelines, metabolic health was defined as having optimal levels of waist circumference (WC <102/88 cm for men/women), glucose (fasting glucose <100 mg/dL and hemoglobin A1c <5.7%), blood pressure (systolic <120 and diastolic <80 mmHg), triglycerides (<150 mg/dL), and high-density lipoprotein cholesterol (≥40/50 mg/dL for men/women), and not taking any related medication.

Results: Changing from ATP III (Adult Treatment Panel III) guidelines to more recent cut points decreased the proportion of metabolically healthy Americans from 19.9% (95% confidence interval [CI]: 18.3–21.5) to 12.2% (95% CI: 10.9–13.6). Dropping WC from the definition increased the percentage of adults with optimal metabolic health to 17.6%. Characteristics associated with greater prevalence of metabolic health were female gender, youth, more education, never smoking, practicing vigorous physical activity, and low body mass in-

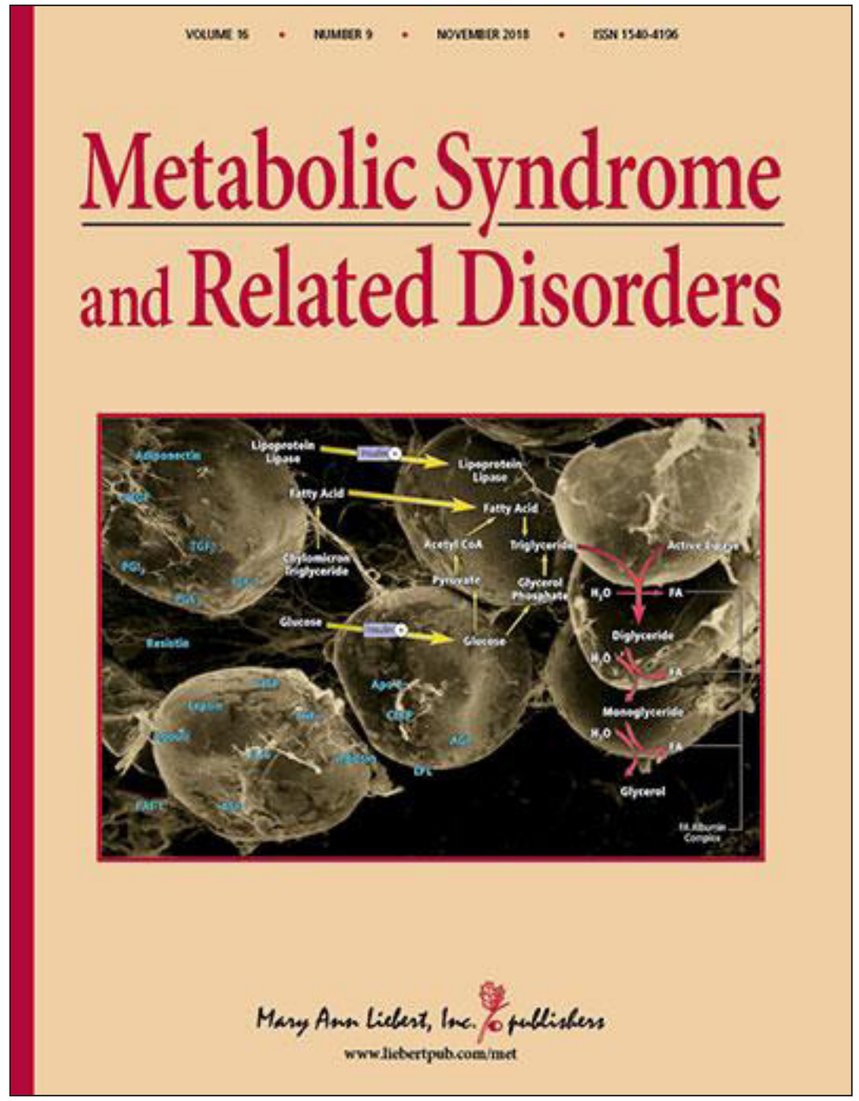
dex. Less than one-third of normal weight adults were metabolically healthy and the prevalence decreased to 8.0% and 0.5% in overweight and obese individuals, respectively.

Conclusions: Prevalence of metabolic health in American adults is alarmingly low, even in normal weight individuals. The large number of people not achieving optimal levels of risk factors, even in low-risk groups, has serious implications for public health.

INTRODUCTION

Since 2001 a number of guidelines have been issued by American scientific societies and government agencies1–7 to provide evidence-based recommendations for cardiometabolic risk factor identification and management. Risk factor cut points indicate levels at which lifestyle and/or pharmaceutical intervention is advised, and provide de facto indicators to define metabolically healthy levels of traditional cardiometabolic risk factors. Currently there is no strong consensus on the combination of variables that define "metabolic health," and different subsets are used in the literature.8–10

We consider metabolic health to be related to, but not the same as, the absence of metabolic syndrome. The 2001 report from the National Cholesterol Education Program Adult Treatment Panel III (ATP III)1 helped to solidify the definition of metabolic syndrome as failing to meet optimal levels of three of five traditional cardiometabolic risk factors. The term metabolic syndrome was coined to point to clusters of risk factors—thus, the stipulation that multiple risk factors must be present. The term "metabolic health" is not aimed at clusters of risk factors, but at identification of a health status characterized by levels of metabolic indicators that are consistent with a high level of health and low risk of impending cardiometabolic disease. The purpose of this research is to determine the number and proportion of American adults who have optimal levels of each of five traditional cardiometabolic risk factors in the absence of pharmaceutical treatment. We examine the impact of the use of cut points proposed by different agencies on these estimates, and show the distributions of metabolic health within demographic and lifestyle categories.



Methods

Study Population

We used data from 2009–2016 National Health and Nutrition Examination Survey (NHANES).11 NHANES is a nationally representative survey of the U.S. noninstitutionalized residents, selected by a complex multistage probability sampling design. The study protocol was approved by the institutional review board at the Centers for Disease Control and Prevention (Atlanta, GA), and written informed consent was obtained from all participants. The analyses included men and nonpregnant women aged ≥20 years who had a fasting blood sample (n = 9447). Participants with missing data on components of the metabolic health definition, body mass index (BMI), physical activity, smoking, or educational level were excluded, and the final sample included 8721 participants.

Data Collection

Data from NHANES participants were collected through questionnaires both at home and in the mobile examination centers (MECs), and examination data, including anthropometrics, were obtained in the MECs, using standardized procedures by trained research staff. Detailed information on data collection is described in NHANES protocols.12 In our analyses of demographic and lifestyle factors we used gender, age, education, race/ethnicity, moderate and vigorous recreational physical activity, smoking, and BMI. Age groups used in the analysis were 20–39, 40–59, and 60 years and over, and race/ethnicity was categorized as non-Hispanic white, non-Hispanic black, Mexican American and other, according to the NHANES analytic guidelines.13 Education was grouped in three categories: less than high school, high school or equivalent, and at least some college. Self-reported data about any current practice of moderate and vigorous recreational physical activity was assessed using yes/no questions, which were then combined to create a three-option variable: none, only moderate, and at least some vigorous physical activity. Regarding smoking, never smokers were those participants who have not smoked at least 100 cigarettes in life, former smokers reported having smoked at least 100 cigarettes in life but do not smoke at all currently, and current smokers are those smoking currently, either everyday or some days. BMI used in the analysis was based on measured weight and height, and subjects were classified in four categories: underweight, <18.5 kg/m2; normal weight, 18.5–24.9 kg/m2; overweight, 25.0–29.9 kg/m2; and obese, ≥30.0 kg/m2.

Regarding the cardiometabolic risk factors, waist circumference (WC) was assessed with a measuring tape at the uppermost lateral border of the right ilium to the nearest 0.1 cm. After resting quietly in a seated position for 5 min, three consecutive blood pressure readings were taken in the right arm. A fourth reading may have been taken, when a measurement was interrupted or incomplete. For the analysis, we used the average of the available readings, excluding the first reading. If only one blood pressure reading was available, that reading was used. Plasma glucose, glycated hemoglobin (HbA1c), triglycerides, and high-density lipoprotein cholesterol (HDL-C) were measured from fasting blood samples. Specific laboratory methods used to quantify each biochemical parameter are described in detail for each survey in NHANES files.14 Medication use for diabetes, blood pressure, and cholesterol was self-reported. Participants with missing data on self-reported medication were considered as not taking medication, if reported no previous medical diagnosis of the disease. The remaining missing values (0.1% for blood pressure medication and 6.6% for cholesterol medication) were included in the denominator, when the prevalence of not taking medication was estimated.

Definition Of Metabolic Health

Prevalence of metabolic health is the proportion of people who have optimal levels of all the risk factor variables without any medication. We first compared the prevalence of metabolic health using cut points from several scientific societies and government agencies.1–6 We then conducted a focused analysis of five risk factors,

grouping variables (e.g., systolic and diastolic blood pressure [SBP and DBP]), and applying cut points using the most recent guidance: (i) WC <102/88 cm in men/women4; (ii) SBP <120 mmHg and DBP <80 mmHg2,5; (iii) glucose <100 mg/dL and HbA1c <5.7%6,7; (iv) triglycerides <150 mg/dL4; (v) HDL-C ≥40/50 mg/dL in men/women.4 We also examined the prevalence of not taking medications for blood pressure, diabetes, and cholesterol.

Statistical Analysis

Associations of optimal metabolic health with gender, age, education, race/ethnicity, physical activity, smoking, and BMI were examined in odds ratios. All analyses accounted for the complex survey design, using the fasting sampling weights and survey procedures (SURVEYFREQ and SURVEYLOGISTIC) in SAS 9.4 (Cary, NC), so estimates are representative of the noninstitutionalized civilian U.S. population. Although <10% of subjects were excluded from our analysis due to missing data (7.7%), we adjusted the NHANES fasting weights according to gender, race/ethnicity, self-reported physical activity, and health insurance.13

Some guidelines5,7 recommend that levels of specific risk factors outside the normal range should be repeated on a separate day to avoid overestimation of risk factors prevalence. Since the NHANES study assessed each participant on only 1 day, we performed sensitivity analyses to examine the impact of correction for within-person day-to-day variability. The gender- and age-specific correction factors from Klungel et al.15 were applied to blood pressure, and the approximate average correction factor (0.8) was applied to glucose, HbA1c, HDL-C, and triglycerides. Since the ratio of the between-person variance to the within-person variance across days is generally smaller for blood pressure than for these other risk factors16–19 the sensitivity analysis was conservative, that is, likely identified more individuals as metabolically healthy than would a true correction.

Results

As expected, the proportion of metabolically healthy Americans changed depending on the cut points applied. Using the cut points from ATP III,1 the overall prevalence of metabolic health was 19.9% (95% confidence interval: 18.3–21.5). It decreased to 16.0% (14.4–17.6) with the reduction of glucose threshold to 100 mg/dL4; to 14.8% (13.2–16.3) with the inclusion of HbA1c in the definition6; and finally to 12.2% (10.9–13.6) when the blood pressure cut points were lowered from 130/85 to 120/80 mmHg for SBP and DBP, respectively.2,5 The 12.2% prevalence corresponds to approximately 27.3 million American adults with optimal metabolic health.

Separate assessments of risk factors showed that <50% of Americans had waist, glucose, and blood pressure levels in the optimal range, whereas almost three-quarters had triglycerides and HDL-C within optimal levels (Table 1). More than 90% reported not taking medication for diabetes, and around 70% did not take medication for blood pressure and cholesterol. In general, women had a higher prevalence of optimal cardiometabolic factors, although this was not true for WC or HDL-C: two risk factors with gender-specific cutoff. With the exception of lipids, the proportion of individuals with optimal risk factor levels tended to decrease with advancing age and higher BMI.

Using this set of the most recent and restrictive cutoffs (Fig. 1), the prevalence of metabolic health was higher in women than men, in those highly educated, who reported currently doing any recreational vigorous physical activity and never smokers; and it decreased markedly with aging. Less than one-third of normal weight adults were metabolically healthy, and the prevalence decreased with increasing BMI. The prevalence of metabolic health was higher among the underweight than in the normal weight; however, the percentage of Americans who are underweight is small and there were only 137 underweight adults in the NHANES unweighted sample. Exclusion of the WC criterion had a relatively large impact on the percentage of obese and overweight adults who were classified as metabolically healthy, increasing the percentages from 0.5% to 6.8% and from 8% to 15.0%, respectively. Nevertheless, the prevalences were still much lower than seen in the normal weight and underweight groups. Removal of the WC criteria changed the overall estimate of optimal metabolic health from 12.2% to 17.6%.

FIG. 1. Population prevalence of optimal metabolic health in American adults, overall and by demographics, physical activity and BMI—NHANES 2009–2016. Hatched segment of bars showing prevalence in BMI categories indicates impact of excluding waist circumference as a criterion. Metabolic health defined as waist circumference <102 cm in men and <88 cm in women; systolic blood pressure <120 mmHg and diastolic blood pressure <80 mmHg; glucose <100 mg/dL and hemoglobin A1c <5.7%; triglycerides <150 mg/dL; high-density lipoprotein cholesterol ≥40 mg/dL in men and ≥50 mg/dL in women; and not taking any lowering medication for blood pressure, glucose, or cholesterol. BMI, body mass index; NHANES, National Health and Nutrition Examination Survey.

Table 2 shows the adjusted odds ratios computed to estimate the independent effects of each of the demographic and lifestyle factors shown in Fig. 1. All of the factors were independently associated with the odds of being metabolically healthy. The association between BMI and metabolic health was attenuated when WC was excluded from the metabolic health definition.

We combined the modifiable characteristics associated with higher or lower odds of metabolic health in a separate analysis to produce maximum contrast. This analysis showed that among normal weight adults, who had at least some college education, reported any vigorous physical activity regularly, and never smoked (population n = 5,660,191), 46.4% enjoyed optimal metabolic health. In contrast, none (0%) had optimal metabolic health if they were obese, had less than a high school education, were not moderately or vigorously active, and were current smokers (population n = 2,777,388).

Correction for short-term variability of the cardiometabolic risk factors hardly changed the estimated prevalence of metabolic health. After correction, prevalence of optimal levels of each factor changed by –0.2 percentage points for glucose metabolism (glucose and HbA1c) to 5.4 for HDL-C. However, the overall prevalence of metabolic health increased by only 1.1 percentage points (from 12.2% to 13.3%).

Discussion

Prevalence of optimal metabolic health is remarkably low among U.S. adults, with one in eight Americans achieving optimal levels of the five traditional cardiometabolic risk factors without medication. To our knowledge, no other study has provided similar estimates of metabolic health, although Muntner et al.20 showed the impact of recent guidelines5 on the prevalence of hypertension. Other reports have described the prevalence of metabolic syndrome10,21 and combinations of risk factors and health behaviors8,22,23 using older data. In NHANES 1999–2004, 7.5% of U.S. adults met criteria that included the absence of smoking, elevated BMI, elevated cholesterol, diabetes, and hypertension.8 Another study applied seven lifestyle and risk factors criteria suggested by the American Heart Association22 to national data from 2011 to 2012 and found that virtually 0% of U.S. adults met all the ideal levels (not smoking, having a healthy diet, sufficient physical activity, normal weight, and normal levels of total cholesterol, blood pressure, and glucose).23 In this work, our focus is on physical manifestations of metabolic health, and we do not include health behaviors in the definition of metabolic health.

The low prevalence of optimal metabolic health was driven by the cut points used. These cut points were selected from prominent scientific societies and government agencies, and are therefore likely to be influential and evidence based. Nevertheless, they may not be entirely immune to advocacy for medication use, even though cutoffs used to identify optimal health are often stricter than those used to screen individuals eligible for pharmaceutical interventions. Recommendations of optimal levels of some risk factors have grown more restrictive for the past two decades as a result of evidence linking levels previously considered optimal to increased risk of cardiovascular disease.5,7,24,25 In this work, we did not consider adults taking medication for blood pressure, diabetes, or cholesterol metabolically healthy, even if cardiometabolic factors were within optimal levels. This option was consistent with the guidelines for the definition of metabolic syndrome.1,3,4

In addition, previous studies have shown that there is residual cardiovascular disease risk in patients treated for elevated blood pressure and cholesterol26–29 compared with adults with similar risk factor levels without pharmacologic treatment. Further, when the medication criteria were removed from the definition, prevalence of optimal metabolic health increased by only 1.2 percentage points.

We recognize that the evidence is weaker for elevated WC as a lone risk factor to define metabolic health compared with the other components; however, it is difficult to justify labeling an adult with any one of the ATP III risk factors as having optimal metabolic health. Since WC is highly correlated with BMI, it is useful to examine associations of BMI with metabolic health with and without WC included in the definition. Dropping WC as a criterion increased the proportion of metabolic health by 5.4 percentage points overall, with greater impact in overweight and obese individuals. Even when WC was excluded from the definition, only one-third of the normal weight adults enjoyed optimal metabolic health. Given the roles of positive energy balance and excess adiposity in the accepted mechanistic genesis of several cardiometabolic risk factors, the metabolically unhealthy normal weight group is perplexing. Normal weight adults are at lower risk than heavier adults for development of cardiometabolic risk factors,30 but as illustrated in this study they are not immune, and it is known that metabolically unhealthy normal weight adults are at increased risk of all-cause mortality and cardiovascular events compared with the metabolically healthy normal weight.31

The use of national data for this analysis is a strength, as was the recalibration of survey weights to better represent the American population. The lack of repeated measure of risk factors over different days was a study limitation, but our sensitivity analysis indicated that this deficit did not have a large impact on prevalence. Finally, cut points for continuous variables are at least somewhat arbitrary, and less strict cut points would result in a greater number of adults labeled as metabolically healthy.

Conclusions

The prevalence of metabolic health in American adults is very low, even in normal weight individuals. The large number of people not achieving optimal cardiometabolic levels of risk factors has serious implications for public health. More work is needed to understand the mechanisms of risk factor development, with attention given to normal weight as well as heavier adults. Most disturbing was the absence of optimal metabolic health in adults who had obesity, less than a high school education, were not physically active, and were current smokers. Currently available interventions to improve health-related behaviors have met with limited success, and stronger and more widely accessible strategies to promote healthier lifestyles are urgently warranted.

Acknowledgment: This study was not funded by any grant or financial support.

Author Disclosure Statement: No conflicting financial interests exist.

Complete References, Graphs & Charts that accompany this report can be found at the following link
(PDF Download at right side of page):
https://www.liebertpub.com/doi/10.1089/met.2018.0105

What is a metabolic disorder

A metabolic disorder occurs when abnormal chemical reactions in your body disrupt your body's metabolism. Metabolism is the process your body uses to get or make energy from the food you eat. Food is made up of proteins, carbohydrates, and fats. Chemicals in your digestive system break the food parts down into sugars and acids, your body's fuel. Your body can use this fuel right away, or it can store the energy in your body tissues, such as your liver, muscles, and body fat.

In a much broader sense, a metabolic disorder is any disease that is caused by an abnormal chemical reaction in your body's cells. Most metabolic disorders involve either abnormal levels of enzymes or hormones, or problems with how those enzymes or hormones work.

If you have a metabolic disorder, the metabolism of your body chemicals is blocked or defective, it can cause a buildup of toxic substances in the body or a lack of substances needed for normal body function, either of which can lead to serious symptoms.

There are different groups of metabolic disorders. Some affect the breakdown of amino acids, carbohydrates, or lipids. Another group like the mitochondrial diseases, affect the parts of the cells that produce the energy.

You can develop a metabolic disorder when some organs, such as your liver or pancreas, become diseased or do not function normally. Diabetes is an example.

Is diabetes a metabolic disorder? Yes.

Metabolic Disorders (The Short List)

Some metabolic disorders are inherited. These are called inborn errors of metabolism. When babies are born, they're tested for many of these in a newborn screening test. Many inborn errors of metabolism can lead to serious complications or even death if they're not controlled with diet or medicine from an early age. However, only 'some' metabolic disorders are inherited, or genetically predisposed, while the vast majority are caused, in the following order, by diet, drinking water contamination, air contamination/pollution, severely depleted soils, lifestyle.

17-alpha-hydroxylase deficiency
17-beta hydroxysteroid dehydrogenase 3 deficiency
18 Hydroxylase deficiency
2-Hydroxyglutaric aciduria
2-methyl-3-hydroxybutyric aciduria
2-methylbutyryl-CoA dehydrogenase deficiency
3 Methylcrotonyl-CoA carboxylase 1 deficiency
3-alpha hydroxyacyl-CoA dehydrogenase deficiency
3-Hydroxyisobutyric aciduria
3-methylcrotonyl-CoA carboxylase deficiency
3-methylglutaconyl-CoA hydratase deficiency (AUH defect)
5-oxoprolinase deficiency
6-pyruvoyl-tetrahydropterin synthase deficiency
Abdominal obesity metabolic syndrome
Abetalipoproteinemia
Acatalasemia

Aceruloplasminemia
Acetyl CoA acetyltransferase 2 deficiency
Acetyl-carnitine deficiency
Acrodermatitis enteropathica
Acromegaly
Acute intermittent porphyria
Adenine phosphoribosyltransferase deficiency
Adenosine deaminase deficiency
Adenosine monophosphate deaminase 1 deficiency
Adenylosuccinase deficiency
Adrenomyeloneuropathy
Adult polyglucosan body disease
Adult-onset citrullinemia type II
Albinism deafness syndrome
Albinism ocular late onset sensorineural deafness
ALG1-CDG (CDG-Ik)
ALG11-CDG (CDG-Ip)
ALG12-CDG (CDG-Ig)
ALG13-CDG
ALG2-CDG (CDG-Ii)
ALG3-CDG (CDG-Id)
ALG6-CDG (CDG-Ic)
ALG8-CDG (CDG-Ih)
ALG9-CDG (CDG-IL)
Alkaptonuria
Alpers syndrome
Alpha-1 antitrypsin deficiency
Alpha-ketoglutarate dehydrogenase deficiency
Alpha-mannosidosis
Aminoacylase 1 deficiency
Anemia due to Adenosine triphosphatase deficiency
Anemia sideroblastic and spinocerebellar ataxia
Apparent mineralocorticoid excess
Arginase deficiency
Argininosuccinic aciduria
Aromatic L-amino acid decarboxylase deficiency
Arthrogryposis renal dysfunction cholestasis syndrome
Arts syndrome
Aspartylglycosaminuria
Ataxia with oculomotor apraxia type 1
Ataxia with vitamin E deficiency
Atransferrinemia
Atypical Gaucher disease due to saposin C deficiency
Autoimmune polyglandular syndrome type 2
Autosomal dominant neuronal ceroid lipofuscinosis 4B
Autosomal dominant optic atrophy and cataract
Autosomal dominant optic atrophy plus syndrome
Autosomal recessive neuronal ceroid lipofuscinosis 4A
Autosomal recessive spastic ataxia 4
Autosomal recessive spinocerebellar ataxia 9
B4GALT1-CDG (CDG-IId)
Bantu siderosis
Barth syndrome
Bartter syndrome
Bartter syndrome antenatal type 1
Bartter syndrome antenatal type 2
Bartter syndrome type 3
Bartter syndrome type 4
Beta ketothiolase deficiency
Biotin-thiamine-responsive basal ganglia disease
Biotinidase deficiency
Bjornstad syndrome
Blue diaper syndrome
Carbamoyl phosphate synthetase 1 deficiency
Carnitine palmitoyl transferase 1 deficiency
Carnitine palmitoyltransferase I deficiency , muscle
Carnitine-acylcarnitine translocase deficiency
Carnosinemia
Central diabetes insipidus
Cerebral folate deficiency
Cerebrotendinous xanthomatosis
Ceroid lipofuscinosis neuronal 1
Chanarin-Dorfman syndrome
Chediak-Higashi syndrome
CHILD syndrome
Childhood hypophosphatasia
Childhood-onset cerebral X-linked adrenoleukodystrophy
Cholesteryl ester storage disease
Chondrocalcinosis 1
Chondrocalcinosis 2
Chondrocalcinosis due to apatite crystal deposition
Chondrodysplasia punctata 1, X-linked recessive
Chronic progressive external ophthalmoplegia
Chylomicron retention disease
Citrulline transport defect
COG1-CDG (CDG-IIg)
COG4-CDG (CDG-IIj)
COG5-CDG (CDG-IIi)
COG7-CDG (CDG-IIe)
COG8-CDG (CDG-IIh)
Combined oxidative phosphorylation deficiency 16
Congenital bile acid synthesis defect, type 1
Congenital bile acid synthesis defect, type 2
Congenital disorder of glycosylation type I/IIX
Congenital dyserythropoietic anemia type 2
Congenital erythropoietic porphyria
Congenital lactase deficiency
Congenital muscular dystrophy-dystroglycanopathy with or without intellectual disability (type B)

Copper deficiency, familial benign
CoQ-responsive OXPHOS deficiency
Crigler Najjar syndrome, type 1
Crigler-Najjar syndrome type 2
Cystinosis
Cystinosis, ocular nonnephropathic
Cytochrome c oxidase deficiency
D-2-hydroxyglutaric aciduria
D-bifunctional protein deficiency
D-glycericacidemia
Danon disease
DCMA syndrome
DDOST-CDG (CDG-Ir)
Deafness, dystonia, and cerebral hypomyelination
Dentatorubral-pallidoluysian atrophy
Desmosterolosis
Diamond-Blackfan anemia
Dicarboxylic aminoaciduria
Dihydrolipoamide dehydrogenase deficiency
Dihydropteridine reductase deficiency
Dihydropyrimidinase deficiency
Dihydropyrimidine dehydrogenase deficiency
Dipsogenic diabetes insipidus
DOLK-CDG (CDG-Im)
Dopa-responsive dystonia
Dopamine beta hydroxylase deficiency
Dowling-Degos disease
DPAGT1-CDG (CDG-Ij)
DPM1-CDG (CDG-Ie)
DPM2-CDG
DPM3-CDG (CDG-Io)
Dubin-Johnson syndrome
Encephalopathy due to prosaposin deficiency
Erythropoietic protoporphyria
Erythropoietic uroporphyria associated with myeloid malignancy
Ethylmalonic encephalopathy
Fabry disease
Familial HDL deficiency
Familial hypocalciuric hypercalcemia type 1
Familial hypocalciuric hypercalcemia type 2
Familial hypocalciuric hypercalcemia type 3
Familial LCAT deficiency
Familial partial lipodystrophy type 2
Fanconi Bickel syndrome
Farber's disease
Fatal infantile encephalomyopathy
Fatty acid hydroxylase-associated neurodegeneration
Fish-eye disease
Fructose-1,6-bisphosphatase deficiency
Fucosidosis
Fukuyama type muscular dystrophy
Fumarase deficiency
Galactokinase deficiency
Galactosialidosis
Gamma aminobutyric acid transaminase deficiency
Gamma-cystathionase deficiency
Gaucher disease
Gaucher disease – ophthalmoplegia – cardiovascular calcification
Gaucher disease perinatal lethal
Gaucher disease type 1
Gaucher disease type 2
Gaucher disease type 3
Gestational diabetes insipidus
Gilbert syndrome – Not a rare disease
Gitelman syndrome
Glucose transporter type 1 deficiency syndrome
Glucose-galactose malabsorption
Glutamate formiminotransferase deficiency
Glutamine deficiency, congenital
Glutaric acidemia type I
Glutaric acidemia type II
Glutaric acidemia type III
Glutathione synthetase deficiency
Glutathionuria
Glycine N-methyltransferase deficiency
Glycogen storage disease 8
Glycogen storage disease type 0, liver
Glycogen storage disease type 12
Glycogen storage disease type 13
Glycogen storage disease type 1A
Glycogen storage disease type 1B
Glycogen storage disease type 3
Glycogen storage disease type 5
Glycogen storage disease type 6
Glycogen storage disease type 7
Glycoproteinosis
GM1 gangliosidosis type 1
GM1 gangliosidosis type 2
GM1 gangliosidosis type 3
GM3 synthase deficiency
GRACILE syndrome
Greenberg dysplasia
GTP cyclohydrolase I deficiency
Guanidinoacetate methyltransferase deficiency
Gyrate atrophy of choroid and retina
Haim-Munk syndrome
Hartnup disease
Hawkinsinuria

Hemochromatosis type 2
Hemochromatosis type 3
Hemochromatosis type 4
Hepatic lipase deficiency
Hepatoerythropoietic porphyria
Hereditary amyloidosis
Hereditary coproporphyria
Hereditary folate malabsorption
Hereditary fructose intolerance
Hereditary hyperekplexia
Hereditary multiple osteochondromas
Hereditary orotic aciduria without megaloblastic anaemia
Hereditary sensory and autonomic neuropathy type 1E
Hereditary sensory neuropathy type 1
Hermansky Pudlak syndrome 2
Histidinemia
HMG CoA lyase deficiency
Homocarnosinosis
Homocysteinemia
Homocystinuria due to CBS deficiency
Homocystinuria due to MTHFR deficiency
Hurler syndrome
Hurler–Scheie syndrome
Hydroxykynureninuria
Hyper-IgD syndrome
Hyperbetaalaninemia
Hypercoagulability syndrome due to glycosylphosphatidylinositol deficiency
Hyperglycerolemia
Hyperinsulinism due to glucokinase deficiency
Hyperinsulinism-hyperammonemia syndrome
Hyperlipidemia type 3
Hyperlipoproteinemia type 5
Hyperlysinemia
Hyperphenylalaninemia due to dehydratase deficiency
Hyperprolinemia
Hyperprolinemia type 2
Hypertryptophanemia
Hypolipoproteinemia
Hypophosphatasia
I cell disease
Imerslund-Grasbeck syndrome
Iminoglycinuria
Inclusion body myopathy 2
Inclusion body myopathy 3
Infantile free sialic acid storage disease
Infantile neuroaxonal dystrophy
Infantile onset spinocerebellar ataxia
Insulin-like growth factor I deficiency
Intrinsic factor deficiency
Isobutyryl-CoA dehydrogenase deficiency
Isovaleric acidemia
Kanzaki disease
Kearns-Sayre syndrome
Krabbe disease atypical due to Saposin A deficiency
L-2-hydroxyglutaric aciduria
L-arginine:glycine amidinotransferase deficiency
Lactate dehydrogenase A deficiency
Lactate dehydrogenase deficiency
Lathosterolosis
LCHAD deficiency
Leber hereditary optic neuropathy
Leigh syndrome, French Canadian type
Lesch Nyhan syndrome
Leucine-sensitive hypoglycemia of infancy
Leukoencephalopathy – dystonia – motor neuropathy
Leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation
Limb-girdle muscular dystrophy type 2I
Limb-girdle muscular dystrophy type 2K – See Limb-girdle muscular dystrophy
Limb-girdle muscular dystrophy type 2M – See Limb-girdle muscular dystrophy
Limb-girdle muscular dystrophy type 2N – See Limb-girdle muscular dystrophy
Limb-girdle muscular dystrophy type 2O – See Limb-girdle muscular dystrophy
Limb-girdle muscular dystrophy type 2T – See Limb-girdle muscular dystrophy
Limb-girdle muscular dystrophy, type 2C
Lipase deficiency combined
Lipoic acid synthetase deficiency
Lipoid proteinosis of Urbach and Wiethe
Lowe oculocerebrorenal syndrome
Lysinuric protein intolerance
Malonyl-CoA decarboxylase deficiency
MAN1B1-CDG
Mannose-binding lectin protein deficiency – Not a rare disease
Mannosidosis, beta A, lysosomal
Maple syrup urine disease type 1A
Maple syrup urine disease type 1B
Maple syrup urine disease type 2
Maternal hyperphenylalaninemia
Maternally inherited diabetes and deafness
Medium-chain acyl-coenzyme A dehydrogenase deficiency
Megaloblastic anemia due to dihydrofolate reductase deficiency

Menkes disease
Metachromatic leukodystrophy
Metachromatic leukodystrophy due to saposin B deficiency
Methionine adenosyltransferase deficiency
Methylcobalamin deficiency cbl G type
Methylmalonic acidemia with homocystinuria type cblC
Methylmalonic acidemia with homocystinuria type cblD
Methylmalonic acidemia with homocystinuria type cblF
Methylmalonic acidemia with homocystinuria type cblJ
Methylmalonic aciduria, cblA type
Methylmalonic aciduria, cblB type
Mevalonic aciduria
MGAT2-CDG (CDG-IIa)
Mild phenylketonuria
Mitochondrial complex I deficiency
Mitochondrial complex II deficiency
Mitochondrial complex III deficiency
Mitochondrial DNA depletion syndrome, encephalomyopathic form with methylmalonic aciduria
Mitochondrial DNA-associated Leigh syndrome
Mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes
Mitochondrial myopathy with diabetes
Mitochondrial myopathy with lactic acidosis
Mitochondrial neurogastrointestinal encephalopathy syndrome
Mitochondrial trifunctional protein deficiency
MOGS-CDG (CDG-IIb)
Mohr-Tranebjaerg syndrome
Molybdenum cofactor deficiency
Monogenic diabetes – Not a rare disease
Morquio syndrome B
MPDU1-CDG (CDG-If)
MPI-CDG (CDG-Ib)
MPV17-related hepatocerebral mitochondrial DNA depletion syndrome
Mucolipidosis III alpha/beta
Mucolipidosis type 4
Mucopolysaccharidosis type II
Mucopolysaccharidosis type III
Mucopolysaccharidosis type IIIA
Mucopolysaccharidosis type IIIB
Mucopolysaccharidosis type IIIC
Mucopolysaccharidosis type IIID
Mucopolysaccharidosis type IVA
Mucopolysaccharidosis type VI
Mucopolysaccharidosis type VII
Multiple congenital anomalies-hypotonia-seizures syndrome
Multiple congenital anomalies-hypotonia-seizures syndrome type 2
Multiple endocrine neoplasia type 2B
Multiple sulfatase deficiency
Multiple symmetric lipomatosis
Muscle eye brain disease
Muscular dystrophy, congenital, megaconial type
Muscular phosphorylase kinase deficiency
Musculocontractural Ehlers-Danlos syndrome
Myoclonic epilepsy with ragged red fibers
Myoglobinuria recurrent
N acetyltransferase deficiency
N-acetyl-alpha-D-galactosaminidase deficiency type III
N-acetylglutamate synthase deficiency
NBIA/DYT/PARK-PLA2G6
Neonatal adrenoleukodystrophy
Neonatal hemochromatosis
Neonatal intrahepatic cholestasis caused by citrin deficiency
Nephrogenic diabetes insipidus
Neu Laxova syndrome
Neuroferritinopathy
Neuronal ceroid lipofuscinosis 10
Neuronal ceroid lipofuscinosis 2
Neuronal ceroid lipofuscinosis 3
Neuronal ceroid lipofuscinosis 5
Neuronal ceroid lipofuscinosis 6
Neuronal ceroid lipofuscinosis 7
Neuronal ceroid lipofuscinosis 9
Neuropathy ataxia retinitis pigmentosa syndrome
Neutral lipid storage disease with myopathy
Niemann-Pick disease type A
Niemann-Pick disease type B
Niemann-Pick disease type C1
Niemann-Pick disease type C2
Northern epilepsy
Not otherwise specified 3-MGA-uria type
Occipital horn syndrome
Ocular albinism type 1
Oculocutaneous albinism type 1
Oculocutaneous albinism type 1B
Oculocutaneous albinism type 2
Oculocutaneous albinism type 3
OPA3 defect
Optic atrophy 1

Ornithine transcarbamylase deficiency
Ornithine translocase deficiency syndrome
Orotic aciduria type 1
Papillon Lefevre syndrome
Parkinson disease type 9
Paroxysmal nocturnal hemoglobinuria
Pearson syndrome
Pentosuria
Permanent neonatal diabetes mellitus
Peroxisomal biogenesis disorders
Peroxisome disorders
Perrault syndrome
Peters plus syndrome
PGM1-CDG
Phosphoglycerate kinase deficiency
Phosphoglycerate mutase deficiency
Phosphoribosylpyrophosphate synthetase deficiency
PMM2-CDG (CDG-Ia)
Pontocerebellar hypoplasia type 6
Porphyria cutanea tarda
Primary carnitine deficiency
Primary hyperoxaluria type 1
Primary hyperoxaluria type 2
Primary hyperoxaluria type 3
Primary hypomagnesemia with secondary hypocalcemia
Progressive external ophthalmoplegia, autosomal recessive 1
Progressive familial intrahepatic cholestasis 1
Progressive familial intrahepatic cholestasis type 2
Progressive familial intrahepatic cholestasis type 3
Prolidase deficiency
Propionic acidemia
Pseudocholinesterase deficiency
Pseudoneonatal adrenoleukodystrophy
Purine nucleoside phosphorylase deficiency
Pycnodysostosis
Pyridoxal 5′ -phosphate-dependent epilepsy
Pyridoxine-dependent epilepsy
Pyruvate carboxylase deficiency
Pyruvate dehydrogenase complex deficiency
Pyruvate dehydrogenase phosphatase deficiency
Pyruvate kinase deficiency
Refsum disease
Refsum disease with increased pipecolic acidemia
Refsum disease, infantile form
Renal glycosuria
Renal hypomagnesemia 2
Renal hypomagnesemia-6
Renal tubulopathy, diabetes mellitus, and cerebellar ataxia due to duplication of mitochondrial DNA
RFT1-CDG (CDG-In)
Rhizomelic chondrodysplasia punctata type 3
Rotor syndrome
Saccharopinuria
Salla disease
Sarcosinemia
Scheie syndrome
Schimke immunoosseous dysplasia
Schindler disease type 1
Schneckenbecken dysplasia
SCOT deficiency
Sea-Blue histiocytosis
Sengers syndrome
Sensory ataxic neuropathy, dysarthria, and ophthalmoparesis
Sepiapterin reductase deficiency
Severe combined immunodeficiency
Short-chain acyl-CoA dehydrogenase deficiency
Sialidosis type I
Sialidosis, type II
Sialuria, French type
Sideroblastic anemia and mitochondrial myopathy
Sitosterolemia
Sjogren-Larsson syndrome
SLC35A1-CDG (CDG-IIf)
SLC35A2-CDG
SLC35C1-CDG (CDG-IIc)
Smith-Lemli-Opitz syndrome
Spastic paraplegia 7
Spinocerebellar ataxia 28
Spinocerebellar ataxia autosomal recessive 3
Spondylocostal dysostosis 1
Spondylocostal dysostosis 2
Spondylocostal dysostosis 3
Spondylocostal dysostosis 4
Spondylocostal dysostosis 6
Spondylodysplastic Ehlers-Danlos syndrome
Spondyloepimetaphyseal dysplasia joint laxity
Spondylothoracic dysostosis
SRD5A3-CDG (CDG-Iq)
SSR4-CDG
Succinic semialdehyde dehydrogenase deficiency
Tangier disease
Tay-Sachs disease
Thiamine responsive megaloblastic anemia syndrome

Thiopurine S methyltranferase deficiency
Tiglic acidemia
TMEM165-CDG (CDG-IIk)
Transaldolase deficiency
Transcobalamin 1 deficiency
Transient neonatal diabetes mellitus
Trehalase deficiency
Trimethylaminuria
Triosephosphate isomerase deficiency
Tyrosine hydroxylase deficiency
Tyrosine-oxidase temporary deficiency
Tyrosinemia type 1
Tyrosinemia type 2
Tyrosinemia type 3
Urea cycle disorders
Valinemia
Variegate porphyria
VLCAD deficiency
Walker-Warburg syndrome
Wilson disease
Wolfram syndrome
Wolman disease
Wrinkly skin syndrome
X-linked adrenoleukodystrophy
X-linked Charcot-Marie-Tooth disease type 5
X-linked creatine deficiency
X-linked dominant chondrodysplasia punctata 2
X-linked sideroblastic anemia
Xanthinuria type 1
Xanthinuria type 2
Zellweger syndrome
Inherited metabolic disorders

Inherited metabolic disorders refer to different types of medical conditions caused by genetic defects — most commonly inherited from both parents — that interfere with the body's metabolism. Inherited metabolic disorders may also be called inborn errors of metabolism.

Metabolism is the complex set of chemical reactions that your body uses to maintain life, including energy production. Special enzymes break down food or certain chemicals so your body can use them right away for fuel or store them. Also, certain chemical processes break down substances that your body no longer needs, or make those it lacks.

When these chemical processes don't work properly due to a hormone or enzyme deficiency, a metabolic disorder occurs. Inherited metabolic disorders fall into different categories, depending on the specific substance and whether it builds up in harmful amounts (because it can't be broken down), it's too low or it's missing.

There are hundreds of inherited metabolic disorders, caused by different genetic defects. Examples include:

Familial hypercholesterolemia, Gaucher disease, Hunter syndrome Krabbe disease Maple syrup urine disease, Metachromatic leukodystrophy, Mitochondrial encephalopathy, lactic acidosis, stroke-like episodes (MELAS)

Niemann-Pick, Phenylketonuria (PKU), Porphyria, Tay-Sachs disease and Wilson's disease. Some metabolic disorders can be diagnosed by routine screening tests done at birth. Others are identified only after a child or adult shows symptoms of a disorder.

Treatment for an inherited metabolic disorder depends on the type and severity of the disorder. Because there are so many types of inherited metabolic disorders, treatment recommendations may vary considerably — from dietary restrictions to liver transplants.

Metabolic Disorders Symptoms
G6PD Deficiency

Glucose-6-phosphate dehydrogenase (G6PD) is just one of the many enzymes that play a role in cell metabolism. G6PD is produced by red blood cells (RBCs) and helps the body metabolize carbohydrates. Without enough normal G6PD to help red blood cells handle certain harmful substances, the cells can be damaged or destroyed, leading to hemolytic anemia. In a process called hemolysis, red blood cells are destroyed prematurely, and the bone marrow (the soft, spongy part of the bone that produces new blood cells) may not be able to produce enough new red blood cells.

Children with G6PD deficiency may be pale and tired and have a rapid heartbeat and breathing. They may also have an enlarged spleen or jaundice (yellowing of the skin and eyes). G6PD deficiency is usually treated by stopping medicines or treating the illness or infection causing the stress on the red blood cells.

Galactosemia

Babies born with this inborn error of metabolism lack the enzyme that converts galactose (one of two sugars found in lactose) into glucose, a sugar the body is able to use. As a result, milk (including breast milk) and other dairy products must be eliminated from the diet. Otherwise, galactose can build up in the system and damage the body's cells and organs, leading to blindness, severe intellectual disability, growth deficiency, and even death.

Hyperthyroidism

This is when an overactive thyroid gland releases too much of the hormone thyroxine, which increases basal metabolic rate (BMR). Your basal metabolic rate (BMR) is a measure of the rate at which your body "burns" energy, in the form of calories, while at rest. Hyperthyroidism causes symptoms such as weight loss, increased heart rate and blood pressure, protruding eyes, and a swelling in the neck from an enlarged thyroid (goiter). Hyperthyroidism may be controlled with medicines or through surgery or radiation treatments.

Hypothyroidism

This is when an absent or underactive thyroid (due to a developmental problem or thyroid disease) causes the release of too little of the hormone thyroxine, which lowers basal metabolic rate (BMR).

If not treated, hypothyroidism can result in stunted growth and intellectual disability in infants and young children. Hypothyroidism slows body processes and causes fatigue (tiredness), slow heart rate, excessive weight gain, and constipation. People with this condition can be treated with oral thyroid hormone.

Phenylketonuria (PKU)

Babies with phenylketonuria (PKU) can't metabolize the amino acid phenylalanine due to a defect in the phenylalanine hydroxylase enzyme. Phenylalanine amino acid, which is found in high-protein foods like breast milk, cow's milk, and meat, is necessary for normal growth in infants and children and for normal protein production. A buildup of phenylalanine amino acid in the bloodstream can affect brain development and lead to intellectual and developmental disability. Symptoms can include delayed mental or social skills, seizures or tremors, hyperactivity, skin rashes (eczema), small head size, and a musty odor in the child's breath, skin, or urine. According to the latest statistics, about one in 10,000 to 15,000 newborns in the United States is diagnosed with PKU each year.

Newborns with phenylketonuria (PKU) initially don't have any symptoms. However, without treatment, babies usually develop signs of PKU within a few months.

Phenylketonuria (PKU) signs and symptoms can be mild or severe and may include:

- A musty odor in the breath, skin or urine, caused by too much phenylalanine in the body
- Neurological problems that may include seizures
- Skin rashes (eczema)
- Fair skin and blue eyes, because phenylalanine can't transform into melanin — the pigment responsible for hair and skin tone
- Abnormally small head (microcephaly)
- Hyperactivity
- Intellectual disability
- Delayed development
- Behavioral, emotional and social problems
- Psychiatric disorders
- Severity varies

The severity of phenylketonuria (PKU) depends on the type. Classic PKU. The most severe form of the disorder is called classic PKU. The enzyme needed to convert phenylalanine is missing or severely reduced, resulting in high levels of phenylalanine and severe brain damage.

Less severe forms of PKU. In mild or moderate forms, the enzyme retains some function, so phenylalanine levels are not as high, resulting in a smaller risk of significant brain damage. But most children with the disorder still require a special PKU diet to prevent intellectual disability and other complications. Early diagnosis and dietary restriction of the amino acid can prevent or lessen the severity of these complications. The best treatment for PKU is a diet of low-protein foods. There are special formulas for newborns. For older children and adults, the diet includes many fruits and vegetables. It also includes some low-protein breads, pastas and cereals. Nutritional formulas provide the vitamins and minerals you can't get from their food.

Type 1 Diabetes

Type 1 diabetes is when your pancreas doesn't produce and secrete enough insulin. Symptoms of type 1 diabetes include excessive thirst and urination, hunger, and weight loss. Over the long term, it can cause kidney problems, pain due to nerve damage, blindness, and heart and blood vessel disease. Kids and teens with type 1 diabetes need to get regular insulin injections and to control their blood sugar levels to reduce the risk of developing complications.

D3 / K2
THE PEER REVIEW

**Supporting
Early Treatment
For CoV-2 Prevents Death
And Hospitalization.**

**The Same Is True For Any Other
Virus Or Even CoV-2 Variants**

Ideally D3 should be taken with K2 and Magnesium. Generally, 5000 IU's of D3 with 93 microgrms of K2 and 400 milligrams of Magnesium per day, with D3 varying based on your levels. I use 10,000 IU's per day. Get Your D3 Checked! Consult With Your Family Physician.

Jan-Feb 2014

Review: Vitamin D3 deficiency results in dysfunctions of immunity with severe fatigue and depression in a variety of diseases

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Recent immune data on vitamin D3 deficiency help to more clearly understand chronic fatiguing illnesses, such as autoimmune disorders, cancer and chronic fatigue syndrome (CFS). The vitamin D3 pathway is activated by stress and requires sufficient stores of precursor 25-hydroxyvitamin D3 for proper cell and immune functions. In vitamin D3 deficiency, secretion of the antimicrobial peptide cathelicidin is reduced, leading to impaired auto/xenophagy. As a result, phagocytosis, cytotoxicity, antigen processing and antigen presentation become dysregulated. In addition, vitamin D3 deficiency affects T- and B-lymphocyte activation, as well as quantity, maturation and function of regulatory natural killer T-cells and their counterparts in the gut, i.e. T-cell receptor-αβ, cluster of differentiation-8αα-positive intraepithelial lymphocytes. Consequently, innate and adaptive immunity become de-regulated, with microbial effects contributing further to this. Persistent infections, chronic inflammation and fatigue follow. Vitamin D3 substitution in such conditions may help to prevent or to ameliorate such chronic conditions, even in patients with cancer.

https://pubmed.ncbi.nlm.nih.gov/24425848/

"Vitamin D3 substitution in such conditions may help to prevent or to ameliorate such chronic conditions [autoimmune disorders and chronic fatigue syndrome (CFS)], even in patients with cancer."

J Steroid Biochem Mol Biol
Epub 2010 Mar 19

Developmental vitamin D3 deficiency induces alterations in immune organ morphology and function in adult offspring

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PMID: 20304054 DOI: 10.1016/j.jsbmb.2010.03.050

Vitamin D3 deficiency and insufficiency are common in women of child-bearing age. This may be cause for concern because vitamin D3 is a well known regulator of immune function and epidemiological evidence has suggested that immune disorders, including autoimmune diseases, could have developmental origins. However, it is not known whether a developmental deficiency in vitamin D3 could lead to persistent changes in the immune system in adult offspring. Given the prominence of receptors for vitamin D3 within immune cells we hypothesised that the developmental absence of vitamin D3 may alter thymic development and thus produce associated functional changes in T cells. We have developed a model of developmental vitamin D3 (DVD) deficiency in Sprague-Dawley rats, in which the vitamin D3 deficiency is transient and restricted to gestation. First we demonstrate that DVD deficiency induced an increase in central but not peripheral immune organ size. Second when stimulated, lymphocytes from DVD-deficient rats exhibit a pro-inflammatory phenotype. This is the first study to show that a transient vitamin D3 deficiency restricted to gestation can persistently alter aspects of immune phenotype and function in the adult offspring. Given an increased incidence of vitamin D3 deficiency in women of child-bearing age these findings may be highly relevant for autoimmune disorders with a developmental basis.

https://pubmed.ncbi.nlm.nih.gov/20304054/

"Given an increased incidence of vitamin D3 deficiency in women of child-bearing age these findings may be highly relevant for autoimmune disorders with a developmental basis."

Med Hypotheses
Epub 2010 Oct 25

Will vitamin D supplementation ameliorate diseases characterized by chronic inflammation and fatigue?

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PMID: 20980105 DOI: 10.1016/j.mehy.2010.09.032

Chronic NF-κB activation has been supposed as a key event in chronic fatigue syndrome (CFS) and many other better-defined pro-inflammatory diseases. Knowledge about the impact of deficiency vitamin D on chronic NF-κB activation could open a new disease approach. Whereas NF-κB activation leads at first to a pro-inflammatory immune response, later on a vitamin D-dependent anti-inflammatory response ensues. Binding of the active vitamin D metabolite 1,25(OH)(2)D(3) to vitamin D receptor (VDR) yields a transcription factor which represses NF-κB activation, and additionally modulates and down-regulates adaptive, but enhances innate immune responses, and improves redox balance, thus counterbalancing inflammation on multiple levels. However, this built-in late counterbalance against inflammation works only when stores of calcium and 25(OH)D(3) are abundant. Therefore a connection between lowered vitamin D-metabolism and persistent NF-κB activation, augmented nitrosative-oxidative stress, redox imbalance, chronic inflammation, and concomitant fatigue can be postulated. In order to confirm this hypothesis, randomized controlled clinical studies about the clinical effects of supplementation of calcium and vitamin D(3) would be necessary in diseases characterized by persistent NF-κB activation and chronic inflammation and fatigue.

https://pubmed.ncbi.nlm.nih.gov/20980105/

"... a connection between lowered vitamin D-metabolism and persistent NF-κB activation, augmented nitrosative-oxidative stress, redox imbalance, chronic inflammation, and concomitant fatigue can be postulated."

Am J Pathol
Epub 2016 Feb 3

1,25-Vitamin D3 Deficiency Induces Albuminuria

By Ramon Sonneveld 1 , Joost G J Hoenderop 2 , Andrea W D Stavenuiter 3 , Evelina Ferrantelli 3 , Marijke P A Baltissen 4 , Henry B Dijkman 5 , Sandrine Florquin 5 , Angelique L Rops 4 , Jack F M Wetzels 4 , Jo H M Berden 4 , Johan van der Vlag 4 , Tom Nijenhuis 6

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PMID: 26851346 DOI: 10.1016/j.ajpath.2015.11.015

Vitamin D plays an important role in renal (patho)physiology. Patients with glomerular diseases have an injured renal filtration barrier, leading to proteinuria and reduced renal function. An impaired renal function also leads to 1,25-vitamin D3 deficiency as a result of reduced renal 1α-hydroxylase activity. Vitamin D treatment to reduce proteinuria remains controversial, although there is an inverse correlation between vitamin D levels and proteinuria. Herein, we showed that 1,25-vitamin D3-deficient 25-hydroxy-vitamin-D3-1α-hydroxylase knockout mice and 1,25-vitamin D3-deficient rats develop podocyte injury and renal dysfunction. Glomerular injury was characterized by proteinuria and partial podocyte foot process effacement. Expression of nephrin, podocin, desmin, and transient receptor potential channel C6 in the podocyte was significantly altered in 1,25-vitamin D3-deficient animals. Supplementation with 1,25-vitamin D3 or 1,25-vitamin D2 prevented podocyte effacement or reversed glomerular and tubulointerstitial damage in 1,25-vitamin D3-deficient animals, thereby preserving and restoring renal function, respectively. The effect of 1,25-vitamin D3 deficiency and 1,25-vitamin D3 and 1,25-vitamin D2 repletion on proteinuria could not be explained by hypocalcemia, changes in parathyroid hormone, or fibroblast growth factor 23. This study demonstrates that 1,25-vitamin D3 deficiency directly leads to renal injury in rodents. Translated to human subjects, this would underline the need for early vitamin D supplementation in patients with glomerular disease and chronic renal insufficiency, which might inhibit or potentially reverse renal injury.

https://pubmed.ncbi.nlm.nih.gov/26851346/

"Translated to human subjects, this would underline the need for early vitamin D supplementation in patients with glomerular disease and chronic renal insufficiency, which might inhibit or potentially reverse renal injury."

J Diabetes Res
Nov 26th, 2020

The Therapeutic Effect of Active Vitamin D Supplementation in Preventing the Progression of Diabetic Nephropathy in a Diabetic Mouse Model

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PMID: 33294462 PMCID: PMC7714593 DOI: 10.1155/2020/7907605

Background: Diabetic nephropathy (DN) is one of the most common microvascular complications of diabetes and is the leading cause of end-stage renal disease (ESRD) and replacement therapy worldwide. Vitamin D levels in DN patients are very low due to the decrease in the synthesis and activity of 1-α hydroxylase in the proximal tubule cells and decrease in the vitamin D receptor abundance. To date, few studies have shown the antioxidant effects of 1α,25-dihydroxyvitamin D3 [1,25(OH)2D3] on hyperglycemia-induced renal injury. The selective activator of the vitamin D receptor, paricalcitol, reduces proteinuria and slows the progression of kidney injury. The precise mechanism through which vitamin D affects diabetic status and provides kidney protection remains to be determined.
Methods: Diabetes mellitus (DM) was induced in 94 8-week-old DBA/2J mice by intraperitoneal injection of streptozotocin (STZ). DM mice were randomly divided into receiving vehicle or treatment with paricalcitol, the active vitamin D analog, 1 week after DM induction or paricalcitol treatment 3 weeks after DM induction. An additional control group of healthy wild-type mice was not treated. Urine albumin, blood urea nitrogen, and creatinine levels were measured before and at the end of the paricalcitol treatment. Periodic acid-Schiff, immunohistochemistry staining, and western blot of the renal tissues of vitamin D receptor, villin, nephrin, and podocin expressions, were analyzed.
Results: Paricalcitol treatment restored villin, nephrin, and podocin protein levels that were downregulated upon DM induction, and reduced fibronectin protein level. Vitamin D receptor activation by paricalcitol may reduce proteinuria of DN in mice and alleviate high-glucose-induced injury of kidney podocytes by regulating the key molecules such nephrin-podocin.
Conclusions: Paricalcitol treatment was associated with improved structural changes in type 1 diabetic mice including upregulation of vitamin D receptor expression, and decreased fibrosis markers such as fibronectin. These effects may contribute to the consistent benefit of vitamin D analog to slow the deterioration in glomerular function and reduce the risk of ESRD in patients with type 1 and 2 diabetes mellitus. Our results suggest that additional use of paricalcitol may be beneficial in treating patients with diabetes under standard therapeutic strategies.

https://pubmed.ncbi.nlm.nih.gov/33294462/

"These effects may contribute to the consistent benefit of vitamin D analog to slow the deterioration in glomerular function and reduce the risk of ESRD in patients with type 1 and 2 diabetes mellitus."

J Clin Orthop Trauma
Epub 2019 Jul 13

Vitamin D for skeletal and non-skeletal health: What we should know

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PMID: 31708633 PMCID: PMC6834997 DOI: 10.1016/j.jcot.2019.07.004

Vitamin D plays an essential role in regulating calcium and phosphate metabolism and maintaining a healthy mineralized skeleton. Humans obtain vitamin D from sunlight exposure, dietary foods and supplements. There are two forms of vitamin D: vitamin D3 and vitamin D2. Vitamin D3 is synthesized endogenously in the skin and found naturally in oily fish and cod liver oil. Vitamin D2 is synthesized from ergosterol and found in yeast and mushrooms. Once vitamin D enters the circulation it is converted by 25-hydroxylase in the liver to 25-hydroxyvitamin D [25(OH)D], which is further converted by the 25-hydroxyvitamin D-1α-hydroxylase in the kidneys to the active form, 1,25-dihydroxyvitamin D [1,25(OH)2D]. 1,25(OH)2D binds to its nuclear vitamin D receptor to exert its physiologic functions. These functions include: promotion of intestinal calcium and phosphate absorption, renal tubular calcium reabsorption, and calcium mobilization from bone. The Endocrine Society's Clinical Practice Guideline defines vitamin D deficiency, insufficiency, and sufficiency as serum concentrations of 25(OH)D of <20 ng/mL, 21-29 ng/mL, and 30-100 ng/mL, respectively. Vitamin D deficiency is a major global public health problem in all age groups. It is estimated that 1 billion people worldwide have vitamin D deficiency or insufficiency. This pandemic of vitamin D deficiency and insufficiency is attributed to a modern lifestyle and environmental factors that restrict sunlight exposure, which is essential for endogenous synthesis of vitamin D in the skin. Vitamin D deficiency is the most common cause of rickets and osteomalacia, and can exacerbate osteoporosis. It is also associated with chronic musculoskeletal pain, muscle weakness, and an increased risk of falling. In addition, several observational studies observed the association between robust levels of serum 25(OH)D in the range of 40-60 ng/mL with decreased mortality and risk of development of several types of chronic diseases. Therefore, vitamin D-deficient patients should be treated with vitamin D2 or vitamin D3 supplementation to achieve an optimal level of serum 25(OH)D. Screening of vitamin D deficiency by measuring serum 25(OH)D is recommended in individuals at risk such as patients with diseases affecting vitamin D metabolism and absorption, osteoporosis, and older adults with a history of falls or nontraumatic fracture. It is important to know if a laboratory assay measures total 25(OH)D or only 25(OH) D3. Using assays that measure only 25(OH)D3 could underestimate total levels of 25(OH)D and may mislead physicians who treat patients with vitamin D2 supplementation.

https://pubmed.ncbi.nlm.nih.gov/31708633/

"vitamin D-deficient patients should be treated with vitamin D2 or vitamin D3 supplementation to achieve an optimal level of serum 25(OH)D."

Review Am J Clin Nutr
December 2004

Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease

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PMID: 15585788 DOI: 10.1093/ajcn/80.6.1678S

Most humans depend on sun exposure to satisfy their requirements for vitamin D. Solar ultraviolet B photons are absorbed by 7-dehydrocholesterol in the skin, leading to its transformation to previtamin D3, which is rapidly converted to vitamin D3. Season, latitude, time of day, skin pigmentation, aging, sunscreen use, and glass all influence the cutaneous production of vitamin D3. Once formed, vitamin D3 is metabolized in the liver to 25-hydroxyvitamin D3 and then in the kidney to its biologically active form, 1,25-dihydroxyvitamin D3. Vitamin D deficiency is an unrecognized epidemic among both children and adults in the United States. Vitamin D deficiency not only causes rickets among children but also precipitates and exacerbates osteoporosis among adults and causes the painful bone disease osteomalacia. Vitamin D deficiency has been associated with increased risks of deadly cancers, cardiovascular disease, multiple sclerosis, rheumatoid arthritis, and type 1 diabetes mellitus. Maintaining blood concentrations of 25-hydroxyvitamin D above 80 nmol/L (approximately 30 ng/mL) not only is important for maximizing intestinal calcium absorption but also may be important for providing the extrarenal 1alpha-hydroxylase that is present in most tissues to produce 1,25-dihydroxyvitamin D3. Although chronic excessive exposure to sunlight increases the risk of nonmelanoma skin cancer, the avoidance of all direct sun exposure increases the risk of vitamin D deficiency, which can have serious consequences. Monitoring serum 25-hydroxyvitamin D concentrations yearly should help reveal vitamin D deficiencies. Sensible sun exposure (usually 5-10 min of exposure of the arms and legs or the hands, arms, and face, 2 or 3 times per week) and increased dietary and supplemental vitamin D intakes are reasonable approaches to guarantee vitamin D sufficiency.

https://pubmed.ncbi.nlm.nih.gov/15585788/

"Although chronic excessive exposure to sunlight increases the risk of nonmelanoma skin cancer, the avoidance of all direct sun exposure increases the risk of vitamin D deficiency, which can have serious consequences."

Review Am J Clin Nutr
April 2008

Vitamin D deficiency: a worldwide problem with health consequences

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PMID: 18400738 DOI: 10.1093/ajcn/87.4.1080S

Vitamin D deficiency is now recognized as a pandemic. The major cause of vitamin D deficiency is the lack of appreciation that sun exposure in moderation is the major source of vitamin D for most humans. Very few foods naturally contain vitamin D, and foods that are fortified with vitamin D are often inadequate to satisfy either a child's or an adult's vitamin D requirement. Vitamin D deficiency causes rickets in children and will precipitate and exacerbate osteopenia, osteoporosis, and fractures in adults. Vitamin D deficiency has been associated with increased risk of common cancers, autoimmune diseases, hypertension, and infectious diseases. A circulating level of 25-hydroxyvitamin D of >75 nmol/L, or 30 ng/mL, is required to maximize vitamin D's beneficial effects for health. In the absence of adequate sun exposure, at least 800-1000 IU vitamin D3/d may be needed to achieve this in children and adults. Vitamin D2 may be equally effective for maintaining circulating concentrations of 25-hydroxyvitamin D when given in physiologic concentrations.

https://pubmed.ncbi.nlm.nih.gov/18400738/

"In the absence of adequate sun exposure, at least 800-1000 IU vitamin D3/d may be needed to achieve this in children and adults. Vitamin D2 may be equally effective for maintaining circulating concentrations of 25-hydroxyvitamin D when given in physiologic concentrations."

Arq Bras Endocrinol Metabol
August 2006

Vitamin D deficiency: A global perspective

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PMID: 17117289 DOI: 10.1590/s0004-27302006000400009

Vitamin D is essential for the maintenance of good health. Its sources can be skin production and diet intake. Most humans depend on sunlight exposure (UVB 290-315 nm) to satisfy their requirements for vitamin D. Solar ultraviolet B photons are absorbed by the skin, leading to transformation of 7-dehydrocholesterol into vitamin D3 (cholecalciferol). Season, latitude, time of day, skin pigmentation, aging, sunscreen use, all influence the cutaneous production of vitamin D3. Vitamin D deficiency not only causes rickets among children but also precipitates and exacerbates osteoporosis among adults and causes the painful bone disease osteomalacia. Vitamin D deficiency has been associated with increased risk for other morbidities such as cardiovascular disease, type 1 and type 2 diabetes mellitus and cancer, especially of the colon and prostate. The prevalence of hypovitaminosis D is considerable even in low latitudes and should be taken into account in the evaluation of postmenopausal and male osteoporosis. Although severe vitamin D deficiency leading to rickets or osteomalacia is rare in Brazil, there is accumulating evidence of the frequent occurrence of subclinical vitamin D deficiency, especially in elderly people.

https://pubmed.ncbi.nlm.nih.gov/17117289/

"Although severe vitamin D deficiency leading to rickets or osteomalacia is rare in Brazil, there is accumulating evidence of the frequent occurrence of subclinical vitamin D deficiency, especially in elderly people."

J Nutr
November 2005

The vitamin D epidemic and its health consequences

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PMID: 16251641 DOI: 10.1093/jn/135.11.2739S

Vitamin D deficiency is now recognized as an epidemic in the United States. The major source of vitamin D for both children and adults is from sensible sun exposure. In the absence of sun exposure 1000 IU of cholecalciferol is required daily for both children and adults. Vitamin D deficiency causes poor mineralization of the collagen matrix in young children's bones leading to growth retardation and bone deformities known as rickets. In adults, vitamin D deficiency induces secondary hyperparathyroidism, which causes a loss of matrix and minerals, thus increasing the risk of osteoporosis and fractures. In addition, the poor mineralization of newly laid down bone matrix in adult bone results in the painful bone disease of osteomalacia. Vitamin D deficiency causes muscle weakness, increasing the risk of falling and fractures. Vitamin D deficiency also has other serious consequences on overall health and well-being. There is mounting scientific evidence that implicates vitamin D deficiency with an increased risk of type I diabetes, multiple sclerosis, rheumatoid arthritis, hypertension, cardiovascular heart disease, and many common deadly cancers. Vigilance of one's vitamin D status by the yearly measurement of 25-hydroxyvitamin D should be part of an annual physical examination.

https://pubmed.ncbi.nlm.nih.gov/16251641/

"There is mounting scientific evidence that implicates vitamin D deficiency with an increased risk of type I diabetes, multiple sclerosis, rheumatoid arthritis, hypertension, cardiovascular heart disease, and many common deadly cancers. Vigilance of one's vitamin D status by the yearly measurement of 25-hydroxyvitamin D should be part of an annual physical examination."

Review South Med J
October 2005

Vitamin D: important for prevention of osteoporosis, cardiovascular heart disease, type 1 diabetes, autoimmune diseases, and some cancers

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PMID: 16295817 DOI: 10.1097/01.SMJ.0000140865.32054.DB

Vitamin D is very important for overall health and wellbeing. A major source of vitamin D comes from exposure to sunlight. Measurement of 25-hydroxyvitamin D in the blood and not 1,25-dihydroxyvitamin D is used to determine vitamin D status. A blood level of 25-hydroxyvitamin D of at least 20 ng/mL is considered to be vitamin D sufficient. Vitamin D deficiency increases the risk of many common cancers, multiple sclerosis, rheumatoid arthritis, hypertension, cardiovascular heart disease, and type I diabetes.

https://pubmed.ncbi.nlm.nih.gov/16295817/

"Vitamin D deficiency increases the risk of many common cancers, multiple sclerosis, rheumatoid arthritis, hypertension, cardiovascular heart disease, and type I diabetes."

Review Adv Exp Med Biol

2014

Sunlight, ultraviolet radiation, vitamin D and skin cancer: how much sunlight do we need?

Michael F Holick
PMID: 25207357

Vitamin D is the sunshine vitamin for good reason. During exposure to sunlight, the UV B photons enter the skin and photolyze 7-dehydrocholesterol to previtamin D3 which in turn is isomerized by the body's temperature to vitamin D3. Most humans have depended on sun for their vitamin D requirement. Skin pigment, sunscreen use, aging, time of day, season and latitude dramatically affect previtamin 13 synthesis. Vitamin D deficiency was thought to have been conquered, but it is now recognized that more than 50% of the world's population is at risk for vitamin D deficiency. This deficiency is in part due to the inadequate fortification of foods with vitamin D and the misconception that a healthy diet contains an adequate amount of vitamin D. Vitamin D deficiency causes growth retardation and rickets in children and will precipitate and exacerbate osteopenia, osteoporosis and increase risk of fracture in adults. The vitamin D deficiency has been associated pandemic with other serious consequences including increased risk of common cancers, autoimmune diseases, infectious diseases and cardiovascular disease. There needs to be a renewed appreciation of the beneficial effect of moderate sunlight for providing all humans with their vitamin D requirement for health.

https://pubmed.ncbi.nlm.nih.gov/25207357/

"The vitamin D deficiency has been associated pandemic with other serious consequences including increased risk of common cancers, autoimmune diseases, infectious diseases and cardiovascular disease."

PLoS One
October 2017

Dietary vitamin D3 deficiency exacerbates sinonasal inflammation and alters local 25(OH)D3 metabolism

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PMID: 29045457 PMCID: PMC5646812 DOI: 10.1371/journal.pone.0186374

Rationale: Patients with chronic rhinosinusitis with nasal polyps (CRSwNP) have been shown to be vitamin D3 (VD3) deficient, which is associated with more severe disease and increased polyp size. To gain mechanistic insights into these observational studies, we examined the impact of VD3 deficiency on inflammation and VD3 metabolism in an Aspergillus fumigatus (Af) mouse model of chronic rhinosinusitis (Af-CRS).
Methods: Balb/c mice were fed control or VD3 deficient diet for 4 weeks. Mice were then sensitized with intraperitoneal Af, and one week later given Af intranasally every three days for four weeks while being maintained on control or VD3 deficient diet. Airway function, sinonasal immune cell infiltrate and sinonasal VD3 metabolism profiles were then examined.
Results: Mice with VD3 deficiency had increased Penh and sRaw values as compared to controls as well as exacerbated changes in sRaw when coupled with Af-CRS. As compared to controls, VD3 deficient and Af-CRS mice had reduced sinonasal 1α-hydroxylase and the active VD3 metabolite, 1,25(OH)2D3. Differential analysis of nasal lavage samples showed that VD3 deficiency alone and in combination with Af-CRS profoundly up-regulated eosinophil, neutrophil and lymphocyte numbers. VD3 deficiency exacerbated increases in monocyte-derived dendritic cell (DC) associated with Af-CRS. Conversely, T-regulatory cells were decreased in both Af-CRS mice and VD3 deficient mice, though coupling VD3 deficiency with Af-CRS did not exacerbate CD4 or T-regulatory cells numbers. Lastly, VD3 deficiency had a modifying or exacerbating impact on nasal lavage levels of IFN-γ, IL-6, IL-10 and TNF-α, but had no impact on IL-17A.
Conclusions: VD3 deficiency causes changes in sinonasal immunity, which in many ways mirrors the changes observed in Af-CRS mice, while selectively exacerbating inflammation. Furthermore, both VD3 deficiency and Af-CRS were associated with altered sinonasal VD3 metabolism causing reductions in local levels of the active VD3 metabolite, 1,25(OH)2D3, even with adequate circulating levels.

https://pubmed.ncbi.nlm.nih.gov/29045457/

"D3 deficiency causes changes in sinonasal immunity, which in many ways mirrors the changes observed in Af-CRS mice, while selectively exacerbating inflammation."

Allergy Rhinol
Epub 2016 Jan 11

Vitamin D deficiency is associated with increased human sinonasal fibroblast proliferation in chronic rhinosinusitis with nasal polyps

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PMID: 26750566 PMCID: PMC4921271 DOI: 10.1002/alr.21704

Background: Vitamin D3 (VD3) is a steroid hormone with known antiproliferative properties. Patients with chronic rhinosinusitis with nasal polyps (CRSwNP) have been shown to be VD3-deficient. Moreover, VD3 deficiency is associated with worse disease in patients with CRSwNP. One cell type thought to play a role in chronic rhinosinusitis (CRS) is the human sinonasal fibroblast (HSNF). The aim of this study was to investigate VD3 deficiency and HSNF proliferation in CRSwNP.
Methods: Blood and sinus tissue explants were collected at the time of surgery from patients with CRSwNP (n = 15). Control subjects (n = 12) were undergoing surgery for cerebrospinal fluid leak repair or to remove non-hormone-secreting pituitary tumors. Ex vivo HSNF proliferation was analyzed with flow cytometry using expression of fibroblast-specific protein (FSP) and the proliferation marker Ki67. Plasma levels of 25-hydroxyvitamin D3 (25VD3) were measured by enzyme-linked immunosorbent assay. In vitro analysis of HSNF proliferation after treatment with calcitriol (1,25VD3) was performed using carboxyfluorescein succinimidyl ester (CFSE) and analyzed with flow cytometry.
Results: In CRSwNP patients there was an inverse correlation between 25VD3 and proliferating HSNFs ($p = 0.0135$). This correlation was not seen for control patients ($p = 0.3869$). In vitro analysis showed that HSNFs from patients with CRSwNP had a higher proliferation index at baseline than HSNFs from control patients ($p < 0.01$). When treated with 1,25VD3, there was a significant decrease in HSNF proliferation index in patients with CRSwNP ($p < 0.01$), but not control patients.
Conclusion: VD3 deficiency is associated with increased HSNF proliferation in CRSwNP. Further investigation into how HSNFs and VD3 impact CRSwNP pathophysiology is warranted.

https://pubmed.ncbi.nlm.nih.gov/26750566/

"VD3 deficiency is associated with increased HSNF proliferation in CRSwNP. Further investigation into how HSNFs and VD3 impact CRSwNP pathophysiology is warranted."

Clin Rheumatol
Epub 2013 Jan 15

Severe deficiency of 25-hydroxyvitamin D_3 (25-OH-D_3) is associated with high disease activity of rheumatoid arthritis

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PMID: 23318705 DOI: 10.1007/s10067-012-2154-6

This study aims to measure the serum level of 25-hydroxyvitamin D_3 (25-OH-D_3) in 302 patients with rheumatoid arthritis (RA), studying the association to disease activity. Three hundred two RA patients underwent clinical examination and serological analysis. 25-Hydroxyvitamin D_3 was determined by high-performance liquid chromatography-tandem mass spectrometry. Vitamin D_3 deficiency defined as serum levels of 25-hydroxyvitamin D_3 below 50 nmol/l was detected in 101 RA patients (33.4 %). There was no significant correlation between the serum level of 25-hydroxyvitamin D_3 and Disease Activity Score 28 (DAS28) (3w) score. In a subpopulation of RA patients with very low serum level of 25-OH-D_3 (≤15 nmol/l) (n = 15), there were significant differences compared to patients with normal 25-OH-D3 (n = 200): higher percentage of patients with positive rheumatoid factor (100.0 versus 77.5 %; p = 0.05), higher CRP (28.7 versus 14.8 mg/l; p = 0.001), higher number of patients treated with at least three disease-modifying antirheumatic drugs (DMARDs) (40.0 versus 14.5 %; p = 0.02), higher number of patients with high disease activity DAS28 score of ≥5.1 (20.0 versus 4.5 %; p = 0.01), lower age (54.5 versus 64.0 years; p = 0.003) and shorter disease duration (5.1 versus 10.3 years; p = 0.06). Deficiency of 25-hydroxyvitamin D_3 was detected in 33.4 % of the RA patients. A subpopulation of patients with severe deficiency of vitamin D_3 serum level of ≤15 nmol/l was characterised by all being positive for rheumatoid factor, high percentage of patients with very high disease activity and high percentage of patients treated with at least three DMARDs.

https://pubmed.ncbi.nlm.nih.gov/23318705/

"A subpopulation of patients with severe deficiency of vitamin D_3 serum level of ≤15 nmol/l was characterised by all being positive for rheumatoid factor, high percentage of patients with very high disease activity and high percentage of patients treated with at least three DMARDs."

Arch Med Sci Atheroscler Dis
July 2020

Silent myocardial dysfunction in vitamin D deficiency

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PMID: 32832715 PMCID: PMC7433788 DOI: 10.5114/amsad.2020.97110

Introduction: Vitamin D (VD) deficiency is a common disease that occurs in all stages of life. A growing number of studies call attention to the relationship between VD deficiency and cardiovascular disease. The aim of this study was to investigate the effect of VD on subclinical left ventricular (LV) function in diabetic and non-diabetic patients with no significant coronary artery disease.
Material and methods: We recruited 140 patients (80 diabetics and 60 non-diabetics) with symptoms of stable ischemic heart disease who underwent coronary angiography and who had no significant coronary artery disease in our clinic. The 25(OH)D3 levels were measured and patients who had 25-(OH)D3 levels below 20 ng/dl were defined as the VD deficient group. In addition to conventional echocardiographic parameters, tissue Doppler echocardiography was used for LV diastolic functions and 2D speckle tracking strain echocardiography (2D STE) for evaluating the longitudinal deformation indices of the LV myocardium.
Results: In all groups, LV global longitudinal strain (GLS) was significantly impaired in patients with VD deficiency ($p < 0.001$) compared to patients without VD deficiency. LV global longitudinal strain rate (GLSR) was significantly impaired in patients with VD deficiency ($p = 0.003$). The GLS was negatively associated with 25-(OH)D3 in the VD deficiency group ($r = -0.52623$, $p < 0.001$). Conversely, GLS was positively associated with 25-(OH)D3 levels in the normal VD group ($r = 0.28$, $p = 0.048$).
Conclusions: VD deficiency is associated with impaired myocardial GLS. The present study demonstrated that VD deficiency may be the cause of subclinical myocardial dysfunction in patients with or without diabetes mellitus and no history of significant coronary artery disease.

https://pubmed.ncbi.nlm.nih.gov/32832715/

"VD deficiency is associated with impaired myocardial GLS. The present study demonstrated that VD deficiency may be the cause of subclinical myocardial dysfunction in patients with or without diabetes mellitus and no history of significant coronary artery disease."

Eurology
Epub 2013 Sep 25

Unrecognized vitamin D3 deficiency is common in Parkinson disease: Harvard Biomarker Study

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PMID: 24068787 PMCID: PMC3888173 DOI: 10.1212/WNL.0b013e3182a95818

Objective: To conclusively test for a specific association between the biological marker 25-hydroxy-vitamin D3, a transcriptionally active hormone produced in human skin and liver, and the prevalence and severity of Parkinson disease (PD).
Methods: We used liquid chromatography/tandem mass spectrometry to establish an association specifically between deficiency of 25-hydroxy-vitamin D3 and PD in a cross-sectional and longitudinal case-control study of 388 patients (mean Hoehn and Yahr stage of 2.1 ± 0.6) and 283 control subjects free of neurologic disease nested in the Harvard Biomarker Study.
Results: Plasma levels of 25-hydroxy-vitamin D3 were associated with PD in both univariate and multivariate analyses with p values = 0.0034 and 0.047, respectively. Total 25-hydroxy-vitamin D levels, the traditional composite measure of endogenous and exogenous vitamin D, were deficient in 17.6% of patients with PD compared with 9.3% of controls. Low 25-hydroxy-vitamin D3 as well as total 25-hydroxy-vitamin D levels were correlated with higher total Unified Parkinson's Disease Rating Scale scores at baseline and during follow-up.
Conclusions: Our study reveals an association between 25-hydroxy-vitamin D3 and PD and suggests that thousands of patients with PD in North America alone may be vitamin D-deficient. This finding has immediate relevance for individual patients at risk of falls as well as public health, and warrants further investigation into the mechanism underlying this association.

https://pubmed.ncbi.nlm.nih.gov/24068787/

"Our study reveals an association between 25-hydroxy-vitamin D3 and PD and suggests that thousands of patients with PD in North America alone may be vitamin D-deficient."

Review Crit Rev Oncol Hematol
Epub 2013 Aug 12

Vitamin D3 insufficiency and colorectal cancer

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PMID: 23941729 DOI: 10.1016/j.critrevonc.2013.07.016

Traditionally the main recognized function of vitamin D has been calcium and phosphate homeostasis. Nevertheless, recent evidences have highlighted the importance of vitamin D3 as a protective agent against various cancers. The association between CRC and vitamin D3 was first suggested in ecologic studies, but further was confirmed by observational studies in humans and experimental studies in both animal models and cellular lines. The protective role of vitamin D3 against cancer has been attributed to its influence of on cell proliferation, differentiation, apoptosis, DNA repair mechanisms, inflammation and immune function. In its active (calcitriol) form (1,25-dihydroxyvitamin D3[1α,25-(OH)2D3]) vitamin D3 and the nuclear vitamin D receptor (VDR) regulate hundreds of genes including those coding for proteins involved in cell differentiation and cell proliferation. The current review addresses some of the key mechanisms that influence the biological actions of vitamin D and its metabolites. The insights derived from these mechanisms may aid in designing new uses for this hormone and its non-hypercalcemic derivatives in the treatment and/or prevention of CRC.

https://pubmed.ncbi.nlm.nih.gov/23941729/

"The protective role of vitamin D3 against cancer has been attributed to its influence of/on cell proliferation, differentiation, apoptosis, DNA repair mechanisms, inflammation and immune function. In its active (calcitriol) form (1,25-dihydroxyvitamin D3[1α,25-(OH)2D3]) vitamin D3 and the nuclear vitamin D receptor (VDR) regulate hundreds of genes including those coding for proteins involved in cell differentiation and cell proliferation."

Review J Steroid Biochem Mol Biol
Epub 2004 Dec 19

The role of Vitamin D3 metabolism in prostate cancer

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PMID: 15663995 DOI: 10.1016/j.jsbmb.2004.10.007

Vitamin D deficiency increases risk of prostate cancer. According to our recent results, the key Vitamin D hormone involved in the regulation of cell proliferation in prostate is 25(OH) Vitamin D3. It is mainly acting directly through the Vitamin D receptor (VDR), but partially also through its 1alpha-hydroxylation in the prostate. A deficiency of 25(OH) Vitamin D is common especially during the winter season in the Northern and Southern latitudes due to an insufficient sun exposure, but Vitamin D deficient diet may partially contribute to it. A lack of Vitamin D action may also be due to an altered metabolism or Vitamin D resistance. Vitamin D resistance might be brought up by several mechanisms: Firstly, an increased 24-hydroxylation may increase the inactivation of hormonal Vitamin D metabolites resulting in a Vitamin D resistance. This is obvious in the cancers in which an oncogenic amplification of 24-hydroxykase gene takes place, although an amplification of this gene in prostate cancer has not yet been described. During the aging, the activity of 24-hydroxylase increases, whereas 1alpha-hydroxylation decreases. Furthermore, it is possible that a high serum concentration of 25(OH)D3 could induce 24-hydroxylase expression in prostate. Secondly, Vitamin D receptor gene polymorphism or defects may result in a partial or complete Vitamin D resistance. Thirdly, an overexpression or hyperphosphorylation of retinoblastoma protein may result in an inefficient mitotic control by Vitamin D. Fourthly, endogenous steroids (reviewed by [D.M. Peehl, D. Feldman, Interaction of nuclear receptor ligands with the Vitamin D signaling pathway in prostate cancer, J. Steroid Biochem. Mol. Biol. (2004)]) and phytoestrogens may modulate the expression of Vitamin D metabolizing enzymes. In summary, the local metabolism of hormonal Vitamin D seems to play an important role in the development and progression of prostate cancer.

https://pubmed.ncbi.nlm.nih.gov/15663995/

"In summary, the local metabolism of hormonal Vitamin D seems to play an important role in the development and progression of prostate cancer."

Am J Physiol Endocrinol Metab
Epub 2020 Nov 11

SARS-CoV-2: influence of phosphate and magnesium, moderated by vitamin D, on energy (ATP) metabolism and on severity of COVID-19

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PMID: 33174766 PMCID: PMC7816430 DOI: 10.1152/ajpendo.00474.2020

The use of vitamin D to reduce the severity of COVID-19 complications is receiving considerable attention, backed by encouraging data. Its purported mode of action is as an immune modulator. Vitamin D, however, also affects the metabolism of phosphate and Mg, which may well play a critical role in SARS-CoV-2 pathogenesis. SARS-CoV-2 may induce a cytokine storm that drains ATP whose regeneration requires phosphate and Mg. These minerals, however, are often deficient in conditions that predispose people to severe COVID-19, including older age (especially males), diabetes, obesity, and usage of diuretics. Symptoms observed in severe COVID-19 also fit well with those seen in classical hypophosphatemia and hypomagnesemia, such as thrombocytopenia, coagulopathy, dysfunction of liver and kidneys, neurologic disturbances, immunodeficiency, failure of heart and lungs, delayed weaning from a respirator, cardiac arrhythmia, seizures, and, finally, multiorgan failure. Deficiencies of phosphate and Mg can be amplified by kidney problems commonly observed in patients with COVID-19 resulting in their wastage into urine. Available data show that phosphate and Mg are deficient in COVID-19, with phosphate showing a remarkable correlation with its severity. In one experiment, patients with COVID-19 were supplemented with a cocktail of vitamin D3, Mg, and vitamin B12, with very encouraging results. We, thus, argue that patients with COVID-19 should be monitored and treated for phosphate and Mg deficiencies, ideally already in the early phases of infection. Supplementation of phosphate and Mg combined with vitamin D could also be implemented as a preventative strategy in populations at risk.

https://pubmed.ncbi.nlm.nih.gov/33174766/

"We, thus, argue that patients with COVID-19 should be monitored and treated for phosphate and Mg deficiencies, ideally already in the early phases of infection. Supplementation of phosphate and Mg combined with vitamin D could also be implemented as a preventative strategy in populations at risk."

Med Clin (Barc)
Epub 2012 Nov 23

Vitamin D deficiency in a Spanish cohort of patients with chronic kidney disease

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PMID: 23182534 DOI: 10.1016/j.medcli.2012.07.026

Background and objective: Vitamin D (25-OH-D3) deficiency is an emerging global health problem. Chronic kidney disease (CKD) patients have a higher risk of this deficiency. We aimed to determine the prevalence of 25-OH-D3 deficiency in a cohort of CKD patients in an urban area of Spain and its relationship with cardiovascular disease (CVD).
Patients and methods: We evaluated the prevalence of 25-OH-D3 deficiency in 751 incident patients referred to our outpatient clinic (male gender 59.3%, mean age 67.2 [± 15] years, mean GFR (MDRD-4) 47.9 ± 25.5 ml/min/1.73 m(2)) with different stages of CKD. We excluded end stage renal disease patients and with kidney transplant. Clinical data and biochemical parameters related to bone and mineral metabolism were recorded. Levels of 25-OH-D3< 15 ng/ml were considered to be deficient.
Results: The mean 25-OH-D3 levels were 17.06 [± 12.93] ng/ml. Only 10% of our patients had adequate 25-OH-D3 levels (>30 ng/ml) and 51% showed deficient levels. 25-OH-D3 deficiency worsened with the progression of CKD (P<.05). Elderly people (P=.001), female gender (P=.02), and diabetes (P=.03) were closely associated with 25-OH-D3 deficiency. 25-OH-D3 deficiency was inversely associated with serum PTH (P=.02), and directly associated with serum calcium (P<.004). Patients with a history of CVD had lower 25-OH-D3 levels (P=.038).
Conclusions: 25-OH-D3 deficiency has a high prevalence in CKD patients, and the severity increases with the progression of kidney disease. Elderly, women and diabetic patients have a higher risk of 25-OH-D3 deficiency. 25-OH-D3 deficiency was related to higher levels of PTH and lower serum calcium.

https://pubmed.ncbi.nlm.nih.gov/23182534/

"Elderly, women and diabetic patients have a higher risk of 25-OH-D3 deficiency. 25-OH-D3 deficiency was related to higher levels of PTH and lower serum calcium."

m J Physiol Gastrointest Liver Physiol
Epub 2015 Sep 3

Dietary vitamin D3 deficiency alters intestinal mucosal defense and increases susceptibility to Citrobacter rodentium-induced colitis

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Free PMC article
Abstract

Vitamin D deficiency affects more that 1 billion people worldwide. Although thought to increase risk of bacterial infections, the importance of vitamin D on host defense against intestinal bacterial pathogens is currently unclear since injection of the active form of vitamin D, 1,25(OH)2D3, increased susceptibility to the enteric bacterial pathogen Citrobacter rodentium by suppressing key immune/inflammatory factors. To further characterize the role of vitamin D during bacteria-induced colitis, we fed weanling mice either vitamin D3-deficient or vitamin D3-sufficient diets for 5 wk and then challenged them with C. rodentium. Vitamin D3-deficient mice lost significantly more body weight, carried higher C. rodentium burdens, and developed worsened histological damage. Vitamin D3-deficient mice also suffered greater bacterial translocation to extra-intestinal tissues, including mesenteric lymph nodes, spleen, and liver. Intestinal tissues of infected vitamin D3-deficient mice displayed increased inflammatory cell infiltrates as well as significantly higher gene transcript levels of inflammatory mediators TNF-α, IL-1β, IL-6, TGF-β, IL-17A, and IL-17F as well as the antimicrobial peptide REG3γ. Notably, these exaggerated inflammatory responses accelerated the loss of commensal microbes and were associated with an impaired ability to detoxify bacterial lipopolysaccharide. Overall, these studies show that dietary-induced vitamin D deficiency exacerbates intestinal inflammatory responses to infection, also impairing host defense.

https://pubmed.ncbi.nlm.nih.gov/26336925/

"Overall, these studies show that dietary-induced vitamin D deficiency exacerbates intestinal inflammatory responses to infection, also impairing host defense."

Otolaryngol Head Neck Surg
Epub 2012 May 24

Vitamin D3 deficiency increases sinus mucosa dendritic cells in pediatric chronic rhinosinusitis with nasal polyps

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Objective: Dendritic cells are professional antigen presenting cells, capable of initiating Th1 or Th2 responses, and have been implicated in the pathogenesis of a number of diseases, including sinusitis. Vitamin D(3) is a steroid hormone that acts on dendritic cells in a manner similar to corticosteroids. Investigators examined whether children with allergic fungal rhinosinusitis (AFRS) or chronic rhinosinusitis with nasal polyposis (CRSwNP) were vitamin D(3) deficient and the relationship of vitamin D(3) deficiency to dendritic cell infiltrate in the sinus mucosa.
Setting: Tertiary care university hospital.
Study design: Retrospective, controlled study using samples collected from pediatric patients seen from August 2009 to July 2011.
Subjects and methods: Plasma levels of 25-hydroxy vitamin D(3) were measured by enzyme-linked immunosorbent assay in children (≤18 years old) with AFRS, CRSwNP, or CRS without nasal polyposis (CRSsNP) and in controls undergoing surgery for adenotonsillar hypertrophy. Vitamin D(3) levels were confirmed using clinical diagnostic methods for those with CRSwNP or AFRS. Tissue samples were immunohistochemically stained for the dendritic cell marker CD209 and the costimulatory molecules CD80 and CD86.
Results: There was no difference in mean vitamin D(3) levels between control and CRSsNP, whereas mean CRSwNP and AFRS levels were both well below the minimum recommended level of 30 ng/mL and significantly lower than control and CRSsNP levels. CD209(+) dendritic cells inversely correlated with vitamin D(3) but not costimulatory molecule expression.
Conclusions: These studies identify that children with CRSwNP or AFRS are vitamin D(3) deficient, which may be linked to increased dendritic cell infiltrate. These results suggest a role for vitamin D(3) as a key player in the immunopathology of pediatric CRSwNP.

https://pubmed.ncbi.nlm.nih.gov/22627120/

" These results suggest a role for vitamin D(3) as a key player in the immunopathology of pediatric CRSwNP."

J Steroid Biochem Mol Biol
Epub 2014 Nov 21

Vitamin D deficiency in pregnant women impairs regulatory T cell function

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Regulatory T cells and IgE receptors (CD23 and CD21) on B cells were assessed in vitamin D deficient pregnant women. For this, 153 pregnant women were recruited from a government hospital and were categorized into three groups based on 25-hydroxyvitamin D3 (25(OH)D3) status. Regulatory T cell population (Treg cells) and CD23/CD21 expression on B cells were quantified by FACS ARIA II in maternal blood at third trimester; and the same parameters were evaluated in cord blood soon after delivery. In addition, TGF β and IL-10 were quantified in maternal and cord blood by using Milliplex kits. In a representative sample of eight women from each group (vitamin D sufficient, insufficient and deficient), placental tissues were processed for mRNA expressions of vitamin D receptor (VDR), retinoic acid receptor (RXR), vitamin D binding protein (VDBP) and vitamin D regulating enzymes. Of the 153 pregnant women, 18 were sufficient (≥30 ng/mL), 55 were insufficient (20-29 ng/mL) and 80 were deficient (≤19 ng/mL) for 25(OH)D3 status. The maternal blood Treg cell population (mean (%)± SE) was lower ($p<0.05$) in 25(OH)D3 deficient (0.2 ± 0.01) pregnant women compared to insufficient (0.34 ± 0.01) and sufficient (0.45 ± 0.02) pregnant women. Similarly, cord blood Treg cell population (mean (%)± SE) was also lower ($p<0.05$) in 25(OH)D3 deficient (0.63 ± 0.03) pregnant women when compared to insufficient (1.05 ± 0.04) and sufficient (1.75 ± 0.02) pregnant women. Mean (%) ± SE of B cells with CD23 and CD21 in maternal blood was higher ($p<0.05$) in 25(OH)D3 deficient pregnant women (0.35 ± 0.02; 1.65 ± 0.04) when compared to insufficient (0.22 ± 0.02; 0.55 ± 0.05) and sufficient (0.15 ± 0.02; 0.21 ± 0.01) pregnant women. Similarly, mean (%)± SE of B cell population with CD23 and CD21 in cord blood was also higher ($p<0.05$) in 25(OH)D3 deficient (0.41 ± 0.02; 1.2 ± 0.03) when compared to insufficient (0.32 ± 0.01; 0.6 ± 0.05) and sufficient (0.2 ± 0.01; 0.4 ± 0.02) pregnant women. Regulatory cytokines, TGF β and IL-10 were lower ($p<0.05$) in 25(OH)D3 insufficient and deficient subjects. In the placenta tissue of women with 25(OH)D3 deficiency, the regulatory T cell transcription factor FOXP3, vitamin D receptor (VDR) and retinoic acid receptor (RXR) expressions were downregulated. In contrast, CD23, CD21 and VDBP expressions were upregulated in 25(OH)D3 deficient and insufficient women. Vitamin D regulating enzymes (CYP24A1, CYP2R1 and CYP27B1) expression were also altered in women with 25(OH)D3 deficiency.

The current study shows that impaired maternal 25(OH)D3 during pregnancy influences the spectrum of immune cells such as regulatory T cells and B cells with IgE receptors and this in turn may be linked to allergy and asthma in neonates.

https://pubmed.ncbi.nlm.nih.gov/25448751/

Korean J Intern Med
Epub 2018 Jun 20

Effect of vitamin D deficiency in Korean patients with acute respiratory distress syndrome

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PMID: 29914229 PMCID: PMC6234412 DOI: 10.3904/kjim.2017.380

Background/aims: Vitamin D modulates innate and adaptive immune responses, and vitamin D deficiency is associated with increased mortality in hospitalized patients with pneumonia. We evaluated the prevalence of vitamin D deficiency in Korean patients with acute respiratory distress syndrome (ARDS) and its effect on the clinical outcomes of ARDS.
Methods: We retrospectively analyzed the data of 108 patients who had a measured serum level of 25-hydroxy vitamin D3 (25(OH)D3) at the time of diagnosis with ARDS. The clinical outcomes were evaluated based on 25(OH)D3 levels of 20 ng/mL and stratified by quartiles of 25(OH)D3 levels.
Results: The mean age of patients was 59.4 years old; 77 (71.3%) were male. Vitamin D deficiency was found in 103 patients (95.4%). The mean 25(OH)D3 level was 8.3 ± 7.0 ng/mL. Neither in-hospital mortality (40.0% vs. 68.0%) nor 6-month mortality (40.0% vs. 71.8%) significantly differed between groups. There were no significant differences in 25(OH)D3 level between survivors (8.1 ± 7.6 ng/mL) and non-survivors (8.5 ± 6.8 ng/mL, p = 0.765). There were no trends toward a difference in mortality among quartiles of 25(OH)D3 levels. However, 25(OH)D3 levels were inversely related with length of hospital stay and intensive care unit stay among in-hospital survivors.
Conclusion: Vitamin D deficiency was prevalent in Korean patients with ARDS. However, levels of vitamin D were not associated with mortality. A large, prospective study is needed to evaluate the effects of vitamin D deficiency on clinical outcomes of ARDS.

https://pubmed.ncbi.nlm.nih.gov/29914229/

"Vitamin D modulates innate and adaptive immune responses, and vitamin D deficiency is associated with increased mortality in hospitalized patients with pneumonia."

Glob Pediatr Health
December 2020

Treatment with Vitamin D3 in Vitamin D Deficient Adolescents: A Pilot Study

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PMID: 33403223 PMCID: PMC7747095 DOI: 10.1177/2333794X20976240

Multiple epidemiological studies have shown that vitamin D deficiency is highly prevalent amongst adolescents in the USA. However, recommendations regarding the treatment of vitamin D deficiency in healthy adolescents are not well defined. We carried out a prospective pilot study, to determine whether treatment with 2000 international units of vitamin D3 daily for 3 months, would normalize the vitamin D levels in vitamin D deficient adolescents. Following treatment there was a 56.02% increase in the vitamin D levels from the mean baseline values and 80.39% of the subjects normalized their vitamin D levels. There were no adverse effects associated with this intervention. This study offers complementary guidelines to the existing recommendations from the American Academy of Pediatrics on the optimal dose and duration of vitamin D3 therapy in vitamin D deficient, but otherwise healthy adolescents. Further prospective, large scale, case control studies are indicated to validate our results.

https://pubmed.ncbi.nlm.nih.gov/33403223/

"Multiple epidemiological studies have shown that vitamin D deficiency is highly prevalent amongst adolescents in the USA."

Behav Brain Res
Epub 2014 Aug 8

Dopamine receptor D3 deficiency results in chronic depression and anxiety

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PMID: 25110304 DOI: 10.1016/j.bbr.2014.07.055

Over the last decade accumulating evidence suggests that brain dopamine (DA) has a role in depression, particularly given the high comorbidity of depression with Parkinson's Disease (PD) and the antidepressant effects of the DA receptor subtype 3 (D3R) agonist pramipexole. The present study assesses the role of D3R in depression. Here we hypothesized that D3R mediates the antidepressant effects of DA. Thus, genetic deficiency of D3R in D3R knockout (D3RKO) mice would yield animals with chronic depressive symptoms. Whereas D3R deficient mice did not show significant alterations in locomotion when tested in the openfield, these animals showed anxiety-like symptoms measured as a significant increase in thigmotaxis at the openfield and a significantly lower time spent in the lit compartment at the light/dark exploration test. D3RKO animals also showed depressive-like symptoms as measured by increased immobility time in the Porsolt forced swim test and the tail suspension test, as well as anhedonia measured in the non-motor dependent sucrose test. In conclusion, D3R deficiency results in anxiety-like and depressive-like symptoms that cannot be attributed to motor dysfunction.

https://pubmed.ncbi.nlm.nih.gov/25110304/

"In conclusion,
D3R deficiency results in
anxiety-like and depressive-like symptoms
that cannot be attributed to motor dysfunction."

J Community Health
October 2011

Prevalence of vitamin D3 deficiency in orange county residents

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PMID: 21327501 DOI: 10.1007/s10900-011-9372-8

With the prevalence of sunlight exposure in Orange County, California, one would expect it to be rare and unusual to find high incidence of Vitamin D deficiencies among its residents. This study evaluated the concentration of Vitamin D3 as part of a larger study to evaluate bone health in Orange County residents. Our preliminary data shows that 19.2% of the 151 subjects evaluated had low Vitamin D3 (<30 pg/ml) and illuminates a growing problem in the United States. We speculate that the widespread sensitivity to skin cancer and sun exposure, the increased use of sun-screens and the filtering of UV waves in automobile glass has put the public at risk for low Vitamin D.

https://pubmed.ncbi.nlm.nih.gov/21327501/

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We speculate that the widespread sensitivity to skin cancer
and sun exposure, the increased use of sun-screens
and the filtering of UV waves in automobile glass
has put the public at risk for low Vitamin D."

PLoS One
Epub 2011 Dec 27

Vitamin D3 deficiency differentially affects functional and disease outcomes in the G93A mouse model of amyotrophic lateral sclerosis

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PMID: 22216257 PMCID: PMC3246470 DOI: 10.1371/journal.pone.0029354

Amyotrophic lateral sclerosis (ALS) is a neuromuscular disease characterized by motor neuron death in the central nervous system. Vitamin D supplementation increases antioxidant activity, reduces inflammation and improves motor neuron survival. We have previously demonstrated that vitamin D(3) supplementation at 10× the adequate intake improves functional outcomes in a mouse model of ALS.

Objective: To determine whether vitamin D deficiency influences functional and disease outcomes in a mouse model of ALS.
Methods: At age 25 d, 102 G93A mice (56 M, 46 F) were divided into two vitamin D(3) groups: 1) adequate (AI; 1 IU D(3)/g feed) and 2) deficient (DEF; 0.025 IU D(3)/g feed). At age 113 d, tibialis anterior (TA), quadriceps (quads) and brain were harvested from 42 mice (22 M and 20 F), whereas the remaining 60 mice (34 M and 26 F) were followed to endpoint.
Results: During disease progression, DEF mice had 25% (P=0.022) lower paw grip endurance AUC and 19% (P=0.017) lower motor performance AUC vs. AI mice. Prior to disease onset (CS 2), DEF mice had 36% (P=0.016) lower clinical score (CS) vs. AI mice. DEF mice reached CS 2 six days later vs. AI mice (P=0.004), confirmed by a logrank test which revealed that DEF mice reached CS 2 at a 43% slower rate vs. AI mice (HR= .57; 95% CI: 0.38, 1.74; P=0.002). Body weight-adjusted TA (AI: r=0.662, P=0.001; DEF: r=0.622, P=0.006) and quads (AI: r=0.661, P=0.001; DEF: r=0.768; P<0.001) weights were strongly correlated with age at CS 2.
Conclusion: Vitamin D(3) deficiency improves early disease severity and delays disease onset, but reduces performance in functional outcomes following disease onset, in the high-copy G93A mouse.

https://pubmed.ncbi.nlm.nih.gov/22216257/

"Vitamin D supplementation increases antioxidant activity, reduces inflammation and improves motor neuron survival."

Review Int J Mol Sci
November 2017

Vitamin D and Neurological Diseases: An Endocrine View

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Vitamin D system comprises hormone precursors, active metabolites, carriers, enzymes, and receptors involved in genomic and non-genomic effects. In addition to classical bone-related effects, this system has also been shown to activate multiple molecular mediators and elicit many physiological functions. In vitro and in vivo studies have, in fact, increasingly focused on the "non-calcemic" actions of vitamin D, which are associated with the maintenance of glucose homeostasis, cardiovascular morbidity, autoimmunity, inflammation, and cancer. In parallel, growing evidence has recognized that a multimodal association links vitamin D system to brain development, functions and diseases. With vitamin D deficiency reaching epidemic proportions worldwide, there is now concern that optimal levels of vitamin D in the bloodstream are also necessary to preserve the neurological development and protect the adult brain. The aim of this review is to highlight the relationship between vitamin D and neurological diseases.

https://pubmed.ncbi.nlm.nih.gov/29160835/

"With vitamin D deficiency reaching epidemic proportions worldwide, there is now concern that optimal levels of vitamin D in the bloodstream are also necessary to preserve the neurological development and protect the adult brain."

ncotarget
January 2017

Vitamin D deficiency is associated with a worse prognosis in metastatic melanoma

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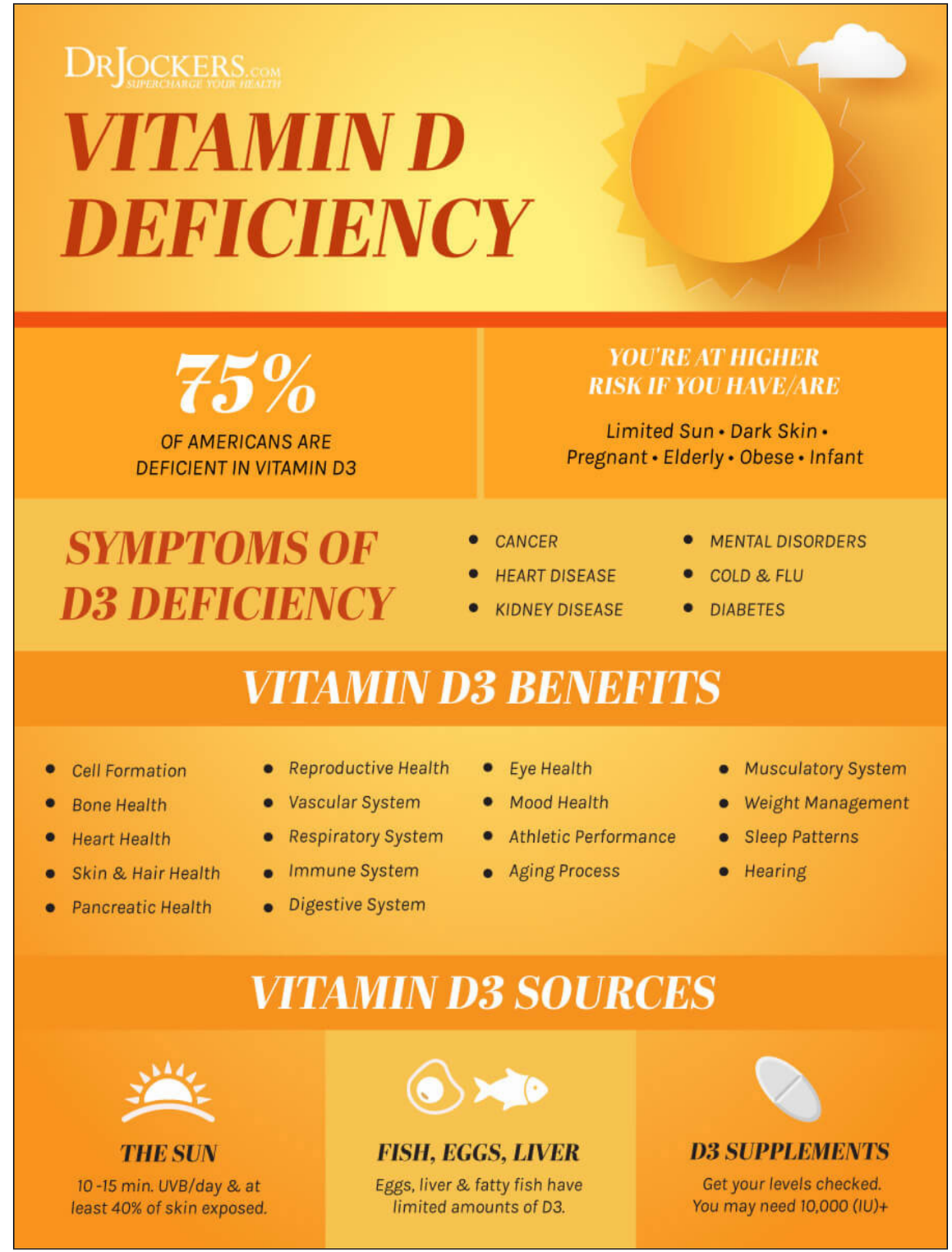
PMID: 28036288 PMCID: PMC5351676 DOI: 10.18632/oncotarget.14316

Vitamin D deficiency (≤20 ng/mL) is associated with an increased incidence and worse prognosis of various types of cancer including melanoma. A retrospective, single-center study of individuals diagnosed with melanoma from January 2007 through June 2013 who had a vitamin D (25(OH)D3) level measured within one year of diagnosis was performed to determine whether vitamin D deficiency and repletion are associated with melanoma outcome. A total of 409 individuals diagnosed with histopathology-confirmed melanoma who had an ever measured serum 25(OH)D3 level were identified. 252 individuals with a 25(OH)D3 level recorded within one year after diagnosis were included in the study and the individual and melanoma characteristics such as age, sex, Breslow thickness, ulceration, stage, mitotic rate, and LDH were obtained from the medical record. A worse melanoma prognosis was associated with vitamin D deficiency (P=0.012), higher stage (P<0.001), ulceration (P=0.001), and higher mitotic rate (P=0.001) (HR 1.93, 95% CI 1.15-3.22). In patients with stage IV metastatic melanoma, vitamin D deficiency was associated with significantly worse melanoma-specific mortality (adjusted HR 2.06, 95% CI 1.10-3.87). Patients with metastatic melanoma who were initially vitamin D deficient and subsequently had a decrease or ≤20 ng/mL increase in their 25(OH)D3 concentration had significantly worse outcomes (HR 4.68, 95% CI 1.05-20.88) compared to non-deficient patients who had a >20 ng/mL increase. Our results suggest that initial vitamin D deficiency and insufficient repletion is associated with a worse prognosis in patients with metastatic melanoma.

https://pubmed.ncbi.nlm.nih.gov/28036288/

"Our results suggest that initial vitamin D deficiency and insufficient repletion is associated with a worse prognosis in patients with metastatic melanoma."



Comparative Study J Mol Cell Cardiol
November 1994

Effect of vitamin D deficiency and 1,25-dihydroxyvitamin D3 on rat heart metabolism

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PMID: 7897666 DOI: 10.1006/jmcc.1994.1161

The purpose of this study was to investigate whether vitamin D3 deficiency and 1,25-dihydroxyvitamin D3 treatment affect some aspects of heart metabolism in the rat. To this end, five experimental groups were studied: (1) the control group of the vitamin D3 supplemented rats (Group A); (2) rachitic rats (Group B); (3) rachitic rats treated with 1,25-dihydroxyvitamin D3 (Group C); (4) rats fed a vitamin D-deficient diet (Group D); (5) rats fed a vitamin D-deficient diet and treated with 1,25-dihydroxyvitamin D3 (Group E). The five groups were compared by checking in the heart some metabolic parameters, i.e. citrate content, and enzyme activities in cytosol and mitochondria. Citrate content was higher in the heart of treated animals when compared with the control. As regards the enzymatic activities in heart mitochondria, NAD(+)-dependent isocitrate dehydrogenase remarkably decreased in Group B rats and 1,25-dihydroxyvitamin D3 restored quite normal values. NADP(+)-dependent isocitrate dehydrogenase decreased in Group B and Group D animals, and 1,25-dihydroxyvitamin D3 treatment was effective in restoring control values. Cytochrome c oxidase activity did not change, while citrate synthase showed an increase in all the treated rats. As regards the cytosolic enzymes, fructose-6-phosphate kinase increased in the two groups of vitamin D-deplete rats in comparison with the control. Glyceraldehyde-3-phosphate dehydrogenase and 3-phosphoglycerate kinase showed a similar trend: an increase in all the treated animals. In heart homogenate, acylphosphatase and acid phosphatase activities were also determined. Acylphosphatase increased in the treated rats, while acid phosphatase decreased in the rats injected with 1,25-dihydroxyvitamin D3. These results support the hypothesis of a participation of 1,25-dihydroxyvitamin D3 in some aspects of heart metabolism.

https://pubmed.ncbi.nlm.nih.gov/7897666/

"These results support the hypothesis of a participation of 1,25-dihydroxyvitamin D3 in some aspects of heart metabolism."

Review Nutr J
June 25, 2013

The beneficial role of vitamin D in obesity: possible genetic and cell signaling mechanisms

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PMID: 23800102 PMCID: PMC3702462 DOI: 10.1186/1475-2891-12-89

The prevalence rates of overweight and obesity are considered an important public issue in the United States, and both of these conditions are increasing among both children and adults. There is evidence of aberrations in the vitamin D-endocrine system in obese subjects. Vitamin D deficiency is highly prevalent in patients with obesity, and many studies have demonstrated the significant effect of calcitriol on adipocytes. Genetic studies have provided an opportunity to determine which proteins link vitamin D to obesity pathology, including the vitamin D receptor, toll-like receptors, the renin-angiotensin system, apolipoprotein E, vascular endothelial growth factor, and poly (ADP-ribose) polymerase-1. Vitamin D also exerts its effect on obesity through cell-signaling mechanisms, including matrix metalloproteinases, mitogen-activated protein kinase pathways, the reduced form of nicotinamide adenine dinucleotide phosphate, prostaglandins, reactive oxygen species, and nitric oxide synthase. In conclusion, vitamin D may have a role in obesity. The best form of vitamin D for use in the obese individuals is calcitriol because it is the active form of the vitamin D_3 metabolite, its receptors are present in adipocytes, and modulates inflammatory cytokine expression.

https://pubmed.ncbi.nlm.nih.gov/23800102/

"In conclusion, vitamin D may have a role in obesity. The best form of vitamin D for use in the obese individuals is calcitriol because it is the active form of the vitamin D_3 metabolite, its receptors are present in adipocytes, and modulates inflammatory cytokine expression."

Review Ther Adv Respir Dis
Epub 2013 Sep 20

Beneficial role of vitamin D3 in the prevention of certain respiratory diseases

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PMID: 24056290 DOI: 10.1177/1753465813503029

There is evidence of aberrations in the vitamin D-endocrine system in subjects with respiratory diseases. Vitamin D deficiency is highly prevalent in patients with respiratory diseases, and patients who receive vitamin D have significantly larger improvements in inspiratory muscle strength and maximal oxygen uptake. Studies have provided an opportunity to determine which proteins link vitamin D to respiratory pathology, including the major histocompatibility complex class II molecules, vitamin D receptor, vitamin D-binding protein, chromosome P450, Toll-like receptors, poly(ADP-ribose) polymerase-1, and the reduced form of nicotinamide adenine dinucleotide phosphate. Vitamin D also exerts its effect on respiratory diseases through cell signaling mechanisms, including matrix metalloproteinases, mitogen-activated protein kinase pathways, the Wnt/β-catenin signaling pathway, prostaglandins, reactive oxygen species, and nitric oxide synthase. In conclusion, vitamin D plays a significant role in respiratory diseases. The best form of vitamin D for use in the treatment of respiratory diseases is calcitriol because it is the active metabolite of vitamin D3 and modulates inflammatory cytokine expression. Further investigation of calcitriol in respiratory diseases is needed.

https://pubmed.ncbi.nlm.nih.gov/24056290/

"In conclusion,

vitamin D plays a significant role in respiratory diseases.

The best form of vitamin D for use in the treatment of respiratory diseases is calcitriol because it is the active metabolite of vitamin D3 and modulates inflammatory cytokine expression. Further investigation of calcitriol in respiratory diseases is needed."

Review J Neurosci Res
Epub 2012 Aug 28

Vitamin D and Parkinson's disease

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PMID: 22930493 DOI: 10.1002/jnr.23115

Parkinson's disease (PD) is the second most common form of neurodegeneration among the elderly population. PD is clinically characterized by tremors, rigidity, slowness of movement, and postural imbalance. Interestingly, a significant association has been demonstrated between PD and low levels of vitamin D in the serum, and vitamin D supplement appears to have a beneficial clinical effect on PD. Genetic studies have provided the opportunity to determine which proteins link vitamin D to PD pathology, e.g., Nurr1 gene, toll-like receptor, gene related to lipid disorders, vascular endothelial factor, tyrosine hydroxylase, and angiogenin. Vitamin D also exerts its effects on cancer through nongenomic factors, e.g., bacillus Calmette-Guerin vaccination, interleukin-10, Wntβ-catenin signaling pathways, mitogen-activated protein kinase pathways, and the reduced form of the nicotinamide adenine dinucleotide phosphate. In conclusion, vitamin D might have a beneficial role in PD. Calcitriol is best used for PD because it is the active form of the vitamin D(3) metabolite and modulates inflammatory cytokine expression. Further investigation with calcitriol in PD is needed.

https://pubmed.ncbi.nlm.nih.gov/22930493/

"In conclusion,

vitamin D might have a beneficial role in PD.

Calcitriol is best used for PD because it is the active form of the vitamin D(3) metabolite and modulates inflammatory cytokine expression."

Review Am J Alzheimers Dis Other Demen
Epub 2011 Dec 27

The beneficial role of vitamin D in Alzheimer's disease

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PMID: 22202127 DOI: 10.1177/1533317511429321
Free article
Abstract

Alzheimer's disease (AD) is the most common form of dementia in the elderly individuals and is associated with progressive neurodegeneration of the human neocortex. Patients with AD have a high prevalence of vitamin D deficiency, which is also associated with low mood and impaired cognitive performance in older people. Genetic studies have provided the opportunity to determine which proteins link vitamin D to AD pathology (ie, the major histocompatibility complex class II molecules, vitamin D receptor, renin-angiotensin system, apolipoprotein E, liver X receptor, Sp1 promoter gene, and the poly(ADP-ribose) polymerase-1 gene). Vitamin D also exerts its effect on AD through nongenomic factors, that is, L-type voltage-sensitive calcium channels, nerve growth factor, the prostaglandins, cyclooxygenase 2, reactive oxygen species, and nitric oxide synthase. In conclusion, vitamin D clearly has a beneficial role in AD and improves cognitive function in some patients with AD. Calcitriol, 1 α,25-dihydroxyvitamin D3, is best used for AD because of its active form of vitamin D(3) metabolite and its receptor in the central nervous system.

https://pubmed.ncbi.nlm.nih.gov/22202127/

"... vitamin D clearly has a beneficial role in AD and improves cognitive function in some patients with AD."

R eview Curr HIV Res
January 2013

The beneficial role of vitamin D in human immunodeficiency virus infection

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PMID: 23170821

Patients with human immuno-deficiency virus (HIV)-infection have a high prevalence of abnormal bone metabolism and vitamin D deficiency. Vitamin D treatment has some benefit in patients with HIV infection. In this paper, we review the evidence for an association between vitamin D and HIV infection. Literature search was done from Medline. Genetic studies have provided the opportunity to determine which proteins link vitamin D to HIV pathology [i.e., the major histocompatibility complex class II molecules, vitamin D receptor, cytochrome P(450), renin-angiotensin system, apoli-poprotein E, liver X receptor, toll-like receptor, poly(ADP-ribosyl) polymerase-1, natural resistance-associated macrophage protein 1, and the Sp1 promoter gene]. Vitamin D also exerts its effect on HIV through nongenomic factors, i.e., ultraviolet radiation exposure, matrix metalloproteinase, heme oxygenase-1, the prostaglandins, cyclooxygenase-2, and oxidative stress. In conclusion, vitamin D may have a beneficial role in HIV. Calcitriol, 1α,25-dihydroxyvitamin D3 should be tested in HIV-infected population because of its active form of the vitamin D3 metabolite and modulates inflammatory cytokine expression. Further investigation with calcitriol in HIV is needed.

https://pubmed.ncbi.nlm.nih.gov/23170821/

"... vitamin D may have a beneficial role in HIV. Calcitriol, 1α,25-dihydroxyvitamin D3 should be tested in HIV-infected population because of its active form of the vitamin D3 metabolite and modulates inflammatory cytokine expression."

Review World J Gastroenterol
October 14, 2012

Theoretical basis of a beneficial role for vitamin D in viral hepatitis

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Affiliations collapse
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PMID: 23082050 PMCID: PMC3471102 DOI: 10.3748/wjg.v18.i38.5338

Abnormal bone metabolism and dysfunction of the calcium-parathyroid hormone-vitamin D axis have been reported in patients with viral hepatitis. Some studies suggested a relationship between vitamin D and viral hepatitis. Genetic studies have provided an opportunity to identify the proteins that link vitamin D to the pathology of viral hepatitis (i.e., the major histocompatibility complex class II molecules, the vitamin D receptor, cytochrome P_{450}, the renin-angiotensin system, apolipoprotein E, liver X receptor, toll-like receptor, and the proteins regulated by the Sp1 promoter gene). Vitamin D also exerts its effects on viral hepatitis via non-genomic factors, i.e., matrix metalloproteinase, endothelial vascular growth factor, prostaglandins, cyclooxygenase-2, and oxidative stress. In conclusion, vitamin D could have a beneficial role in viral hepatitis. Calcitriol is best used for viral hepatitis because it is the active form of the vitamin D_3 metabolite.

https://pubmed.ncbi.nlm.nih.gov/23082050/

"In conclusion, vitamin D could have a beneficial role in viral hepatitis. Calcitriol is best used for viral hepatitis because it is the active form of the vitamin D_3 metabolite."

Neuroepidemiology
Epub 2011 Dec 7

Vitamin D-mentia: randomized clinical trials should be the next step

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PMID: 22156654 DOI: 10.1159/000334177

Hypovitaminosis D is highly prevalent in the elderly. Its possible role in the pathogenesis of Alzheimer's disease (AD) is particularly important, as AD remains a public health concern with no current efficient treatment. Vitamin D administration could be a multitarget stabilizing treatment for AD since vitamin D simultaneously targets several factors leading to neurodegeneration through immunoregulatory, antioxidant and anti-ischemic actions, as well as the regulation of neurotrophic factors, acetylcholine neurotransmitter and clearance of amyloid beta peptide, and the avoidance of hyperparathyroidism. By preventing neuronal loss, the question is whether correcting hypovitaminosis D among older adults could also prevent AD-related cognitive decline. The cross-sectional associations between the vitamin D intakes--whether from diet, sun exposure or drug supplements--and cognition strengthened this hypothesis, but prevented the finding of a cause and effect link. Pre-post studies showed an improvement of cognition concomitant with the increase in 25-hydroxyvitamin D concentrations. One randomized trial found that supraphysiological doses of vitamin D were not better than physiological doses at improving cognition in AD. At this stage, only clinical trials testing vitamin D supplements versus placebo can further determine the impact of vitamin D administration on cognition and AD with higher levels of evidence.

https://pubmed.ncbi.nlm.nih.gov/22156654/

"Vitamin D administration could be a multitarget stabilizing treatment for AD since vitamin D simultaneously targets several factors leading to neurodegeneration through immunoregulatory, antioxidant and anti-ischemic actions, as well as the regulation of neurotrophic factors, acetylcholine neurotransmitter and clearance of amyloid beta peptide, and the avoidance of hyperparathyroidism."

Review J Steroid Biochem Mol Biol
Epub 2013 Feb 13

Vitamin D status and gene transcription in immune cells

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PMID: 23416105 DOI: 10.1016/j.jsbmb.2013.02.005

Background: Vitamin D is a modulator of the immune system. Its insufficiency has been implicated in type 1 diabetes (T1D) and studies showed significant associations with polymorphisms of vitamin D genes. Aim of the study was to investigate whether gene expression in immune cells, vitamin D status and genetic variants are correlated in healthy controls (HC).
Methods: From 23 HC monocytes (Mo), T-helper cells (Th) and natural killer cells (NK) were isolated. In all immune cells gene expression of vitamin D receptor (VDR), 25-vitamin-D-hydroxylase (CYP2R1) and 25-hydroxyvitamin-D3-1a-hydroxylase (CYP27B1) were measured by Taqman assay. Furthermore, CYP2R1 (rs10741657), CYP27B1 (rs10877012) and the VDR-FokI (rs10735810) polymorphisms in HC were genotyped. Finally, 25-hydroxyvitamin D3 (25(OH)D3) and 1,25-dihydroxyvitamin D3 (1,25(OH)2D3) plasma levels in HC were measured by radioimmunoassay.
Results: All studied immune cells showed a significantly different gene expression of CYP2R1 and CYP27B1 (p=1×10(-6), respectively). When stratifying the HC according to vitamin D deficiency and vitamin D sufficiency, within the 25(OH)D3 deficient group significantly lower 1,25(OH)2D3 plasma levels (p=0.02) in HC and a significant down-regulation of the VDR expression only in Mo were observed (p=0.04). Furthermore, a significant correlation between CYP2R1 gene transcription and 1,25(OH)2D3 plasma levels in Th cells was found (p=0.04). No associations between the gene expression levels and the investigated polymorphism in all different immune cells were detected. However, vitamin D deficiency in combination with the "AC" CYP27B1 genotype appeared to inhibit the CYP27B1 expression in NK cells (p=0.03).
Conclusion: Both 25(OH)D3 deficiency and low 1,25(OH)2D3 levels appear to interact with its system gene transcription illustrating the relevance for targeted vitamin D therapy. This article is part of a Special Issue entitled 'Vitamin D Workshop'.

https://pubmed.ncbi.nlm.nih.gov/23416105/

"Vitamin D is a modulator of the immune system.
Both 25(OH)D3 deficiency and low 1,25(OH)2D3 levels
appear to interact with its system gene transcription
illustrating the relevance for targeted vitamin D therapy."

Einstein (Sao Paulo)
Oct-Dec 2014

Serum level of vitamin D3 in cutaneous melanoma

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PMID: 25628199 PMCID: PMC4879914 DOI: 10.1590/S1679-45082014AO3090

Objective: To compare the level of vitamin D3 in cutaneous melanoma patients, with or without disease activity, with reference values and with patients from a general hospital.
Methods: The serum levels of vitamin D3 were measured in cutaneous melanoma patients, aged 20 to 88 years, both genders, from January 2010 to December 2013. The samples from the general group were processed at Hospital Israelita Albert Einstein (control group). Data analysis was performed using the Statistics software.
Results: A total of 100 patients were studied, 54 of them men, with mean age of 54.67 years, and 95 Caucasian. Out of these 100 patients, 17 had active disease. The average levels of vitamin D3 in the melanoma patients were lower than the level considered sufficient, but above the average of the control group. Both groups (with or without active disease) of patients showed a similar distribution of vitamin D3 deficiency.
Conclusion: Vitamin D3 levels in melanoma patients were higher than those of general patients and lower than the reference level. If the reference values are appropriate, a large part of the population had insufficient levels of vitamin D, including those with melanoma, or else, this standard needs to be reevaluated. No difference in vitamin D3 levels was found among melanoma patients with or without active disease. More comprehensive research is needed to assess the relation between vitamin D and melanoma.

https://pubmed.ncbi.nlm.nih.gov/25628199/

"If the reference values are appropriate, a large part of the
population had insufficient levels of vitamin D, including
those with melanoma, or else, this standard
needs to be reevaluated."

Medicine (Baltimore)
March 2015

Vitamin D deficiency is an independent risk factor for urinary tract infections after renal transplants

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PMID: 25738483 PMCID: PMC4553964 DOI: 10.1097/MD.0000000000000594

Vitamin D deficiency is frequently found in patients with renal transplants (RTxs). Because vitamin D plays indispensable roles in the immune system, there may be an association between vitamin D deficiency and infection in these patients, but this has not been fully elucidated. Therefore, this study investigated the impact of pre-RTx vitamin D deficiency on urinary tract infection (UTI) development after RTx.We measured 25-hydroxyvitamin D3 (25(OH)D3) levels in 410 patients 2 weeks before they underwent RTx. Vitamin D deficiency was defined as 25(OH)D3 <10 ng/mL. The primary outcome was UTI occurrence after RTx. Cox proportional hazard analysis determined whether vitamin D deficiency was independently associated with UTI.The mean 25(OH)D3 level was 12.8 ± 6.9 ng/mL, and 171 patients (41.7%) were vitamin D deficient. During a median follow-up duration of 7.3 years, the UTI incidence was significantly higher in vitamin D-deficient patients (52 patients, 30.4%) compared with vitamin D-nondeficient patients (40 patients, 16.7%) (P = 0.001). Moreover, multivariate Cox proportional hazard analysis showed that vitamin D deficiency was an independent predictor of UTI after RTx (hazard ratio 1.81, 95% confidence interval 1.11-2.97, P = 0.02).Vitamin D deficiency was an independent risk factor for UTI after RTx; hence, determining 25(OH)D3 levels might help to predict infectious complications after RTx.

https://pubmed.ncbi.nlm.nih.gov/25738483/

"Because vitamin D plays indispensable roles in the immune system, there may be an association between vitamin D deficiency and infection in these patients, but this has not been fully elucidated."

r J Clin Nutr
Epub 2020 Mar 3

CYP27B1 as an instrument gene to investigate the causal relationship between vitamin D deficiency and obesity: a family-based study

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Objectives: Vitamin D deficiency was associated with obesity. However, the causal relationship remains controversial. We hypothesized that there would be family-based associations in both vitamin D deficient families and obese families for the SNPs associated with vitamin D deficiency, if vitamin D deficiency was a causal factor of obesity. We aimed to investigate the family-based association of SNPs in CYP27B1 with both vitamin D deficiency and obesity.
Methods: Four hundred and nineteen pedigrees containing 1505 rural individuals aged from 18 to 79 years in Henan Province of China were included in this study. Family-based associations of rs10877012 and rs4646536 in CYP27B1 with vitamin D deficiency and obesity were investigated. Serum 25(OH)D3 concentration <20 μg/L was defined as vitamin D deficiency. BMI ≥ 28 kg/m2 was applied for obesity definition. Taqman assays were applied for SNP genotyping. Family-based associations were investigated with FBAT software.
Results: It was shown that vitamin D deficiency was a risk factor of obesity (adjusted OR: 1.332, 95% CI: 1.042-1.703, P = 0.022). Furthermore, there were family-based associations for allele T of rs10877012 and allele T of rs4646536 in both vitamin D deficient families and obese families (P < 0.05). Both rs10877012 and rs4646536 were associated with serum 25(OH)D3 levels between siblings (P < 0.05), but not BMI (P > 0.05). In addition, there is linkage disequilibrium between rs10877012 and rs4646536 (D' = 1.0, r2 = 0.992).
Conclusion: Vitamin D deficiency may be a causal factor of obesity. Maintaining sufficient vitamin D is beneficial to obesity prevention.

https://pubmed.ncbi.nlm.nih.gov/32127688/

"Vitamin D deficiency may be a causal factor of obesity. Maintaining sufficient vitamin D is beneficial to obesity prevention."

Review Int J Paleopathol
Epub 2018 Mar 13

The pathology of vitamin D deficiency in domesticated animals: An evolutionary and comparative overview

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PMID: 29544996 DOI: 10.1016/j.ijpp.2018.03.001

Although vitamin D is critical to calcium/phosphorus homeostasis, bone formation and remodeling, there is evolution-based variation between species in vitamin D metabolism and susceptibility to rickets and osteomalacia. Most herbivores produce vitamin D3 in response to sunlight, but dogs and cats have generally lost the ability as carnivore diets are rich in vitamin D. Nutritional deficiencies and/or poor exposure to sunlight can induce rickets in birds, swine, cattle and sheep, but horses are less susceptible as they have evolved a calcium homeostasis that is quite different than other animals. Adaptations to specific environments also affect disease incidence: llamas/alpacas out of their natural high altitude intense solar radiation environments are highly susceptible to vitamin D deficiency. The pathology of rickets/osteomalacia is similar across species, however fibrous osteodystrophy is more common and may also be present. Rickets/osteomalacia were likely more common in animals before the advent of commercial diets, but can be difficult to definitively diagnose especially in single archeological specimens. Consideration of species susceptibility, location - especially in terms of latitude, and any available information on diet, season of occurrence, husbandry practices or descriptions of affected animals can support the diagnosis of metabolic bone disease in animals.

https://pubmed.ncbi.nlm.nih.gov/29544996/

"Nutritional deficiencies and/or poor exposure to sunlight can induce rickets in birds, swine, cattle and sheep, but horses are less susceptible as they have evolved a calcium homeostasis that is quite different than other animals."

J Autism Dev Disord
September 2020

The Association Between Serum Vitamin D3 Levels and Autism Among Jordanian Boys

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PMID: 30993503 DOI: 10.1007/s10803-019-04017-w

This study assesses the correlation between vitamin-D deficiency and autism spectrum disorder (ASD) in Jordan. We performed a case-controlled cross-sectional analysis to assess vitamin D levels in 83 children with ASD aged less than 8 years old compared to 106 healthy controls. In addition, the association between vitamin D deficiencies and gastrointestinal (GI) complains and electroencephalogram (EEG) abnormalities commonly found in children with ASD was investigated. Vitamin D levels in ASD patients were significantly lower. Also, Vitamin D levels in ASD patients had significant correlation with GI complains, but no correlation between vitamin D levels and Ca2+or EEG abnormalities was detected. These data suggest a possible role for vitamin D deficiency in the pathophysiology of ASD.

https://pubmed.ncbi.nlm.nih.gov/30993503/

"This study assesses the correlation between vitamin-D deficiency and autism spectrum disorder (ASD) in Jordan. These data suggest a possible role for vitamin D deficiency in the pathophysiology of ASD."

Int J Biochem Cell Biol
Epub 2019 Dec 9

Vitamin D deficiency induces the excitation/inhibition brain imbalance and the proinflammatory shift

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PMID: 31821883 DOI: 10.1016/j.biocel.2019.105665

Vitamin D3 is among the major neurosteroids whose role in developing and adult brain is intensively studied now. Its active form 1,25(OH)2D3 regulates the expression and functioning of a range of brain-specific proteins, which orchestrate the neurotransmitter turnover, neurogenesis and neuroplasticity. Despite numerous studies of the vitamin D role in normal and pathological brain function, there is little evidence on the mechanisms of alterations in excitatory and inhibitory neurotransmission under vitamin D deficiency (VDD). Using the animal model we characterized the dysfunction of excitatory and inhibitory neurotransmission under alimentary VDD. The shift between unstimulated and evoked GABA release under VDD was largely reversed after treatment of VDD, whereas the impairments in glutamatergic system were only partially recovered after 1-month vitamin D3 supplementation. The increase of the external glutamate level and unstimulated GABA release in brain nerve terminals was associated with intensified ROS production and higher [Ca2+]i in presynapse. The negative allosteric modulation of presynaptic mGlu7 receptors significantly enhanced exocytotic GABA release, which was decreased under VDD, thereby suggesting the neuroprotective effect of such modulation of inhibitory neurotransmission. Synaptic plasma membranes and cytosolic proteins contribute to the decreased stimulated release of neurotransmitter, by being the crucial components, whose functional state is impaired under VDD. The critical changes with synaptic vesicles occurred at the docking step of the process, whereas malfunctioning of synaptic cytosolic proteins impacted the fusion event foremost. The decreased amplitude of exocytosis was inherent for non-excitable cells as well, as evidenced by lower platelet degranulation. Our data suggest the presynaptic dysfunction and proinflammatory shift as the early events in the pathogenesis of VDD-associated disorders and provide evidences for the neuroprotective role of vitamin D3.

https://pubmed.ncbi.nlm.nih.gov/31821883/

"Our data suggest the presynaptic dysfunction and proinflammatory shift as the early events in the pathogenesis of VDD-associated disorders and provide evidences for the neuroprotective role of vitamin D3."

Review Am J Clin Nutr
December 2004

Vitamin D status, 1,25-dihydroxyvitamin D3, and the immune system

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Vitamin D is an important immune system regulator. The active form of vitamin D, 1,25-dihydroxyvitamin D3 [1,25(OH)2D3], has been shown to inhibit the development of autoimmune diseases, including inflammatory bowel disease (IBD). Paradoxically, other immune system-mediated diseases (experimental asthma) and immunity to infectious organisms were unaffected by 1,25(OH)2D3 treatment. There are similar paradoxical effects of vitamin D deficiency on various immune system functions. Vitamin D and vitamin D receptor (VDR) deficiency resulted in accelerated IBD. Experimental asthma was unaffected by 1,25(OH)2D3 treatment and was less severe among VDR-deficient mice. Vitamin D is a selective regulator of the immune system, and the outcome of 1,25(OH)2D3 treatment, vitamin D deficiency, or VDR deficiency depends on the nature of the immune response (eg, infectious disease, asthma, or autoimmune disease). An additional factor that determines the effect of vitamin D status on immune function is dietary calcium. Dietary calcium has independent effects on IBD severity. Vitamin D-deficient mice on low-calcium diets developed the most severe IBD, and 1,25(OH)2D3 treatment of mice on low-calcium diets improved IBD symptoms. However, the best results for IBD were observed when the calcium concentration was high and 1,25(OH)2D3 was administered. Both the type of immune response and the calcium status of the host determine the effects of vitamin D status and 1,25(OH)2D3 on immunity.

https://pubmed.ncbi.nlm.nih.gov/15585793/

"Vitamin D is an important immune system regulator. The active form of vitamin D, 1,25-dihydroxyvitamin D3 [1,25(OH)2D3], has been shown to inhibit the development of autoimmune diseases ..."

Med Clin (Barc)
Epub 2019 May 24

An epidemiology survey of vitamin D deficiency and its influencing factors

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PMID: 31133232 DOI: 10.1016/j.medcli.2019.03.019

Background: There is growing evidence that vitamin D is related to the development of a variety of diseases. The current study was performed to investigate the status of serum vitamin D distribution among adult Chinese people and reveal the influence of gender, age, seasonality and residential regions on serum vitamin D levels.
Method: This cross-sectional study included 14,302 participants aged from 18 years old to 65 years old from six major cities in China. The basic demographic information and the levels of serum vitamin D (25(OH)D) and vitamin D3 (25(OH)D3) were collected from Jan 2, 2014 to Dec 25, 2017.
Result: The prevalence of 25(OH)D3 concentration <30ng/mL reached up to 83%, in which the rate of vitamin D insufficiency (20-29ng/mL) was 32.7%, and vitamin D deficiency (10-19ng/mL) accounted for 41.9%, and vitamin D severe shortage (<10ng/mL) accounted for 8.4%. Women were more likely to have vitamin D3 deficiency and lower serum vitamin D3 concentration than men (both p<0.001). The mean concentration of serum 25(OH)D and 25(OH)D3 in summer and autumn were higher than that in spring and winter (p<0.001), and the mean concentration of serum 25(OH)D in people from Southern China was higher than that in people from other regions (p<0.001). Although the mean concentrations of serum 25(OH)D and 25(OH)D3 were both increased by age, the percentage of patients with serum 25(OH)D3 insufficiency was also increased.
Conclusion: Serum vitamin D deficiency is very common in adults in China. The level of serum vitamin D may be associated with age, sex, seasonality and residential regions.

https://pubmed.ncbi.nlm.nih.gov/31133232/

"Serum vitamin D deficiency is very common in adults in China. The level of serum vitamin D may be associated with age, sex, seasonality and residential regions."

Clin Nutr
Epub 2015 Jun 6

High prevalence of vitamin D deficiency in urban health checkup population

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PMID: 26093537 DOI: 10.1016/j.clnu.2015.05.019

Background: Vitamin D deficiency is documented as a common health problem in the world. Limited data has been found on the prevalence of vitamin D deficiency in Beijing area.
Aim: To investigate the prevalence s of vitamin D deficiency in urban Beijing residents and the seasonal and monthly serum 25(OH)D variation in this population.
Methods: This is an urban hospital based cross-sectional study lasting whole 2 years. 5531 (5-101 years old) urban Beijing residents for health checkup are recruited from December 9th, 2011 to December 8th, 2013. Each subject completed a questionnaire designed to quantify intake of vitamin D through food, vitamin D supplements, hours of sun exposure, sunscreen use over the past month. Serum 25(OH)D is statistically analyzed in accordance with gender, age, and time-lines.
Results: Vitamin D deficiency (Serum 25(OH)D level ≤20 ng/mL) and sever deficiency (Serum 25(OH)D level ≤ 10 ng/mL) are highly prevalent in this population. The prevalence of vitamin D deficiency is 87.1% and higher prevalence is found in female (89.0%) than male (84.9% P < 0.001). Severe vitamin D deficiency is also higher in female than male (59.3% and 42.7%, respectively, P < 0.001). Female under 20 and over 80 have lower 25(OH)D levels compared to 40-60 years old female (both P < 0.05). Severe vitamin D deficiency are also highly prevalence in this two group (60.9% and 54.1%) compared with 40-60 years old females (43.1%, both P < 0.05). Seasonal variation are also found in this population (P < 0.01). Autumn and summer have the higher 25(OH) D level than winter and spring in both genders (P < 0.001). Winter and spring have higher vitamin D deficiency and Severe deficiency than the other two seasons (P < 0.05). Serum 25(OH)D level peaks in October and troughed in April in both female and male. Lower serum 25(OH)D level are found in April than February (P < 0.05) in both gender.
Conclusions: This is the first time to examine the prevalence of vitamin D deficiency among urban Beijing residents spanning the age spectrum. And Vitamin D deficiency and severe deficiency is found highly prevalent in this population, especially among females under 20 and older than 80 and in winter and spring seasons.

Targeted prevention on vitamin D deficiency is urgent for this population.

https://pubmed.ncbi.nlm.nih.gov/26093537/

J Steroid Biochem Mol Biol
Epub 2019 Nov 19

Higher risk of vitamin D insufficiency/deficiency for rural than urban dwellers

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PMID: 31756419 DOI: 10.1016/j.jsbmb.2019.105547

There are many risk factors for Vitamin D deficiency. This study aimed to compare the Vitamin D status and serum 25(OH)D concentrations of adults living in an urban area to adults living in a rural area in the West of Ireland (latitude 53.27° North). A cross-sectional retrospective analysis of clinical records was performed. Following interrogation of the electronic laboratory information system, individuals who had serum 25(OH) D concentrations measured at Galway University Hospitals between January 2011 and December 2015 were identified. Clinical demographics, setting and date of sampling were recorded. In total, 17,590 patients (urban n = 4,824; rural n = 12,766) were eligible for inclusion. Serum 25(OH)D concentrations were lower among rural compared to urban dwellers irrespective of season (spring $p < 0.001$, summer $p = 0.009$, autumn $p = 0.002$, winter $p < 0.001$). There was a significant difference in Vitamin D status between urban and rural dwellers in three of the four seasons: spring- deficiency: 16%-v-23%, insufficiency: 39%-v-43%, sufficiency: 45%-v-35% ($p < 0.001$); autumn- deficiency: 11%-v-10%, insufficiency: 30%-v-35%, sufficiency: 59%-v-56% ($p = 0.01$); winter- deficiency: 23%-v-25%, insufficiency: 35%-v-42%, sufficiency: 41%-v-33% ($p < 0.001$). Serum 25(OH)D concentrations were higher and the prevalence of deficiency lower in urban/rural females compared to urban/rural males ($p < 0.001$). Serum 25(OH)D concentrations increased sequentially from the 18-39 year age group to the 60-69 year age group in both urban ($p < 0.001$) and rural ($p < 0.001$) dwellers and then decreased progressively as age increased to ≥90 years. The odds of Vitamin D deficiency increased with age, lower daily sunshine hours, male gender, rural address and season.

https://pubmed.ncbi.nlm.nih.gov/31756419/

"There are many risk factors for Vitamin D deficiency. The odds of Vitamin D deficiency increased with age, lower daily sunshine hours, male gender, rural address and season."

J Pediatr Gastroenterol Nutr
May 2014

Seasonal vitamin D status of healthy schoolchildren and predictors of low vitamin D status

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PMID: 24787093 DOI: 10.1097/MPG.0000000000000274

Objectives: The aim of the study was to assess seasonal prevalence of vitamin D deficiency according to sex and to determine the relations between serum levels of 25-hydroxyvitamin D [25(OH)D] and parathyroid hormone (PTH) and sociodemographic characteristics in otherwise healthy schoolchildren during spring and autumn.
Methods: In a cross-sectional study, 746 healthy students aged between 11 and 18 years were recruited during spring (n = 375) and autumn (n = 371). Sociodemographic data were collected by a questionnaire. Serum 25(OH)D, PTH, calcium, phosphate, and alkaline phosphatase were measured. Serum 25(OH)D levels were categorized as <50 nmol/L (vitamin D deficiency) and <25 nmol/L (severe deficiency).
Results: Mean ± standard deviation 25(OH)D levels were 22.3 ± 10.5 nmol/L in girls and 28.5 ± 17.0 nmol/L in boys during spring ($P < 0.001$) and 36.5 ± 20.3 nmol/L in girls and 45.0 ± 18.5 nmol/L in boys during autumn ($P < 0.001$). The prevalence of vitamin D deficiency was 93% during spring and 71% during autumn. There was a negative correlation between 25(OH)D and PTH levels ($P < 0.01$). We determined a cutoff point of serum 25(OH)D in which the mean serum PTH concentration began to increase as 35.8 nmol/L ($P < 0.0001$). The age, sex, and calcium level were found to be independent predictors for vitamin D deficiency.
Conclusions: Vitamin D deficiency is prevalent among healthy schoolchildren. It is noteworthy that 25(OH) D levels were significantly lower in girls and during autumn. We recommend vitamin D supplementation for children in addition to more time spent for outdoor activities for sensible sunlight exposure.

https://pubmed.ncbi.nlm.nih.gov/24787093/

"Vitamin D deficiency is prevalent among healthy schoolchildren. It is noteworthy that 25(OH)D levels were significantly lower in girls and during autumn. We recommend vitamin D supplementation for children in addition to more time spent for outdoor activities for sensible sunlight exposure."

BMC Public Health
September 26, 2014

Vitamin D levels in an Australian population

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PMID: 25256413 PMCID: PMC4194387 DOI: 10.1186/1471-2458-14-1001

Background: Levels of vitamin D in the population have come under increasing scrutiny, however there are only a few studies in Australia which measure levels in the general population. The aim of this study was to measure the levels of vitamin D within a large population cohort and examine the association with seasons and selected demographic and health risk factors.
Methods: A longitudinal cohort study of 2413 participants in the northwest suburbs of Adelaide, South Australia conducted between 2008 and 2010 was used to examine serum levels of 25-hydroxy vitamin D (25(OH) D) in relation to demographic characteristics (age, sex, income, education and country of birth), seasons, the use of vitamin D supplements and selected health risk factors (physical activity, body mass index and smoking). Both unadjusted and adjusted mean levels of serum 25(OH)D were examined, as were the factors associated with the unadjusted and adjusted prevalence of serum 25(OH)D levels below 50 and 75 nmol/L.
Results: Overall, the mean level of serum 25(OH)D was 69.2 nmol/L with 22.7% of the population having a serum 25(OH)D level below 50 nmol/L, the level which is generally recognised as vitamin D deficiency. There were significantly higher levels of 25(OH)D among males compared to females ($t = 4.65$, $p < 0.001$). Higher levels of 25(OH)D were also measured in summer and autumn compared with winter and spring. Generally, mean levels of 25(OH)D were lower in those classified as obese. Smokers and those undertaking no or less than 150 minutes/week of physical activity also had lower levels of serum vitamin D. Obesity (as classified by body mass index), season and undertaking an insufficient level of physical activity to obtain a health benefit were significantly associated with the prevalence of vitamin D deficiency.
Conclusions: Vitamin D deficiency is prevalent in South Australia, affecting almost one quarter of the population and levels are related to activity, obesity and season even when adjusted for confounding factors. Improved methods of addressing vitamin D levels in population are required.

https://pubmed.ncbi.nlm.nih.gov/25256413/

"Vitamin D deficiency is prevalent in South Australia, affecting almost one quarter of the population and levels are related to activity, obesity and season even when adjusted for confounding factors."

Nutr Hosp
April1, 2015

Prevalence of vitamin d deficiency and insuffiency and associated factors in pregnant women of northern Spain

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PMID: 25795951 DOI: 10.3305/nh.2015.31.4.8448

Background and objectives: The vitamin D deficiency during pregnancy has been associated with adverse events during pregnancy and the postnatal child development. In this study we examined plasma levels of vitamin D [25(OH)D3] and factors associated with plasma deficiency and insufficiency in pregnant women in northern Spain.
Methods: We analyzed data from 453 pregnant women participating in the INMA-Asturias cohort in which was determined 25(OH)D3 by high resolution liquid chromatography.Dietary intake of vitamin D was estimated through a food frequency validated questionnaire. We estimated the prevalence of deficiency [25(OH)D3 <20 ng/ml] and insufficiency [20 to 29.9 ng / ml] of vitamin D and analyzed the distribution of 25(OH)D3 per month extraction and other factors.
Results: The mean concentration of 25(OH)D3 was 27.7 ng/ml (range 6.4 to 69.5). 27.4% of pregnant women had deficient levels and 35.3% inssuficient. Levels of 25(OH)D3 were higher in the summer months (median 34.1 ng/ml). There was a higher percentage of deficiency in pregnant women with overweight/obesity (34.5%) and under 25 years (47.8%). The average daily intake of vitamin D was 5.48 mg / day (SD 2.82 range 1.09 to 32.52).Intake during the months of October to May was associated with levels of 25(OH)D3. 8.6% reported taking supplements of vitamin D.
Conclusions: We detected a high proportion of pregnant women with deficient or insufficient vitamin D levels, especially in the months of October to May, in pregnant women with overweight and obesity, and the youngest.

https://pubmed.ncbi.nlm.nih.gov/25795951/

"We detected a high proportion of pregnant women with deficient or insufficient vitamin D levels, especially in the months of October to May, in pregnant women with overweight and obesity, and the youngest."

Review Nutrients
July 5, 2018

The Association of Vitamin D Levels with Common Pregnancy Complications

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The association between vitamin D deficiency and various adverse pregnancy outcomes has been extensively investigated in recent years. The pregnant woman is the only source of vitamin D for the foetus. The main sources of vitamin D for pregnant women are sunlight, fortified dairy products, oily fish and dietary supplements. Vitamin D deficiency during pregnancy has been associated with some adverse neonatal outcomes as well as an increased risk of late pregnancy complications. The outcomes of the published studies investigating preeclampsia and gestational diabetes mellitus vary with some large trials suggesting a potential positive effect of vitamin D supplementation during pregnancy on the decreased risk of these complications. Research also suggests a possible connection between lower vitamin D concentrations and increased risk of preterm labour. In our manuscript, we aim to review the existing literature regarding the prevalence of vitamin D deficiency during pregnancy, the factors associated with vitamin D deficiency, and possible pregnancy complications arising from it.

https://pubmed.ncbi.nlm.nih.gov/29976852/

"Vitamin D deficiency during pregnancy
has been associated with some adverse neonatal outcomes
as well as an increased risk of
late pregnancy complications."

Brain Res Bull
March 15, 2005

Developmental Vitamin D3 deficiency alters the adult rat brain

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PMID: 15763180 DOI: 10.1016/j.brainresbull.2004.12.007

There is growing evidence that Vitamin D(3) (1,25-dihydroxyvitamin D(3)) is involved in brain development. We have recently shown that the brains of newborn rats from Vitamin D(3) deficient dams were larger than controls, had increased cell proliferation, larger lateral ventricles, and reduced cortical thickness. Brains from these animals also had reduced expression of nerve growth factor (NGF) and glial cell line-derived neurotrophic factor. The aim of the current study was to examine if there were any permanent outcomes into adulthood when the offspring of Vitamin D(3) deficient dams were restored to a normal diet. The brains of adult rats were examined at 10 weeks of age after Vitamin D(3) deficiency until birth or weaning. Compared to controls animals that were exposed to transient early Vitamin D(3) deficiency had larger lateral ventricles, reduced NGF protein content, and reduced expression of a number genes involved in neuronal structure, i.e. neurofilament or MAP-2 or neurotransmission, i.e. GABA-A(alpha4). We conclude that transient early life hypovitaminosis D(3) not only disrupts brain development but leads to persistent changes in the adult brain. In light of the high incidence of hypovitaminosis D(3) in women of child-bearing age, the public health implications of these findings warrant attention.

https://pubmed.ncbi.nlm.nih.gov/15763180/

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of these findings warrant attention."

Review J Steroid Biochem Mol Biol
May 2004

Vitamin D3-implications for brain development

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PMID: 15225838 DOI: 10.1016/j.jsbmb.2004.03.070

There is growing evidence that 1,25-dihydroxyvitamin D(3) (1,25(OH)(2)D(3)) is active in the brain but until recently there was a lack of evidence about its role during brain development. Guided by certain features of the epidemiology of schizophrenia, our group has explored the role of 1,25(OH)(2)D(3) in brain development using whole animal models and in vitro culture studies. The expression of the vitamin D receptor (VDR) in the embryonic rat brain rises steadily between embryonic day 15-23, and 1,25(OH)(2)D(3) induces the expression of nerve growth factor and stimulates neurite outgrowth in embryonic hippocampal explant cultures. In the neonatal rat, low prenatal vitamin D(3) in utero leads to increased brain size, altered brain shape, enlarged ventricles, reduced expression of nerve growth factors, reduced expression of the low affinity p75 receptor and increased cellular proliferation. In summary, there is growing evidence that low prenatal levels of 1,25(OH)(2)D(3) can influence critical components of orderly brain development. It remains to be seen if these processes are of clinical relevance in humans, but in light of the high rates of hypovitaminosis D in pregnant women and neonates, this area warrants further scrutiny.

https://pubmed.ncbi.nlm.nih.gov/15225838/

"In the neonatal rat, low prenatal vitamin D(3) in utero leads to increased brain size, altered brain shape, enlarged ventricles, reduced expression of nerve growth factors, reduced expression of the low affinity p75 receptor and increased cellular proliferation.

In summary, there is growing evidence that low prenatal levels of 1,25(OH)(2)D(3) can influence critical components of orderly brain development."

Review Prog Biophys Mol Biol
Epub 2006 Feb 28

Vitamin D Physiology

P Lips 1

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PMID: 16563471 DOI: 10.1016/j.pbiomolbio.2006.02.016

Vitamin D3 is synthesized in the skin during summer under the influence of ultraviolet light of the sun, or it is obtained from food, especially fatty fish. After hydroxylation in the liver into 25-hydroxyvitamin D (25(OH) D) and kidney into 1,25-dihydroxyvitamin D (1,25(OH)2D), the active metabolite can enter the cell, bind to the vitamin D-receptor and subsequently to a responsive gene such as that of calcium binding protein. After transcription and translation the protein is formed, e.g. osteocalcin or calcium binding protein. The calcium binding protein mediates calcium absorption from the gut. The production of 1,25(OH)2D is stimulated by parathyroid hormone (PTH) and decreased by calcium. Risk factors for vitamin D deficiency are premature birth, skin pigmentation, low sunshine exposure, obesity, malabsorption and advanced age. Risk groups are immigrants and the elderly. Vitamin D status is dependent upon sunshine exposure but within Europe, serum 25(OH)D levels are higher in Northern than in Southern European countries. Severe vitamin D deficiency causes rickets or osteomalacia, where the new bone, the osteoid, is not mineralized. Less severe vitamin D deficiency causes an increase of serum PTH leading to bone resorption, osteoporosis and fractures. A negative relationship exists between serum 25(OH)D and serum PTH. The threshold of serum 25(OH)D, where serum PTH starts to rise is about 75nmol/l according to most surveys. Vitamin D supplementation to vitamin D-deficient elderly suppresses serum PTH, increases bone mineral density and may decrease fracture incidence especially in nursing home residents. The effects of 1,25(OH)2D and the vitamin D receptor have been investigated in patients with genetic defects of vitamin D metabolism and in knock-out mouse models. These experiments have demonstrated that for active calcium absorption, longitudinal bone growth and the activity of osteoblasts and osteoclasts both 1,25(OH)2D and the vitamin D receptor are essential. On the other side, bone mineralization can occur by high ambient calcium concentration, so by high doses of oral calcium or calcium infusion. The active metabolite 1,25(OH)2D has its effects through the vitamin D receptor leading to gene expression, e.g. the calcium binding protein or osteocalcin or through a plasma membrane receptor and second messengers such as cyclic AMP. The latter responses are very rapid and include the effects on the pancreas, vascular smooth muscle and monocytes. Muscle cells contain vitamin D receptor and several studies have demonstrated that serum 25(OH)D is related to physical performance. The active metabolite 1,25(OH)2D has an antiproliferative effect and downregulates inflammatory markers. Extrarenal synthesis of 1,25(OH)2D occurs under the influence of cytokines and is important for the paracrine regulation of cell differentiation and function. This may explain that vitamin D deficiency can play a role in the pathogenesis of auto-immune diseases such as multiple sclerosis and diabetes type 1, and cancer. In conclusion, the active metabolite 1,25(OH)2D has pleiotropic effects through the vitamin D receptor and vitamin D responsive elements of many genes and on the other side rapid non-genomic effects through a membrane receptor and second messengers. Active calcium absorption from the gut depends on adequate formation of 1,25(OH)2D and an intact vitamin D receptor. Bone mineralization mainly depends on ambient calcium concentration.

Vitamin D metabolites may play a role in the prevention of auto-immune disease and cancer.

https://pubmed.ncbi.nlm.nih.gov/16563471/

Am J Physiol
December 1987

Involvement of vitamin D3 with cardiovascular function. II. Direct and indirect effects

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PMID: 2827502 DOI: 10.1152/ajpendo.1987.253.6.E675

To determine whether the changes in cardiovascular function that accompany vitamin D3 deficiency are the direct result of hypovitaminosis D3 or a response to the hypocalcemia that accompanies vitamin D3 deficiency, rats were maintained for 9 wk on a vitamin D3-deficient diet containing either low (0.4%) calcium or high (2.5%) calcium to prevent hypocalcemia. Rats were also maintained on the low-calcium, vitamin D3-deficient diet for 9 wk and then transferred to diets designed to reverse hypocalcemia or vitamin D3 deficiency. The results demonstrate that the changes in in vitro cardiac contractile function that accompany vitamin D3 deficiency 1) could not be prevented by preventing the hypocalcemia that normally accompanies vitamin D3 depletion or 2) could not be reversed by restoration of serum calcium to normal levels after the initial period of vitamin D3 depletion. In contrast, the change in in vitro vascular muscle contractile function observed in vitamin D3-deficient, hypocalcemic rats could be prevented by maintaining serum calcium at normal levels and also reversed by restoration of serum calcium to normal after an initial period of vitamin D3 deficiency. These observations indicate that hypocalcemia does not account for the changes in cardiac contractile function that result from vitamin D3 depletion and suggest a direct role for vitamin D3 or its metabolite 1,25-dihydroxyvitamin D3 in regulating cardiac contractility. Possible mechanisms underlying this direct effect were also explored.

https://pubmed.ncbi.nlm.nih.gov/2827502/

"These observations indicate that hypocalcemia does not account for the changes in cardiac contractile function that result from vitamin D3 depletion and suggest a direct role for vitamin D3 or its metabolite 1,25-dihydroxyvitamin D3 in regulating cardiac contractility."

Am J Physiol
January 1990

Involvement of vitamin D3 with cardiovascular function. III. Effects on physical and morphological properties

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PMID: 2154115 DOI: 10.1152/ajpendo.1990.258.1.E134

We have previously shown that depletion of vitamin D3 in rats results in a large increase in the contractile function of isolated hearts (R. E. Weishaar, J. Clin. Invest. 79: 1706-1712, 1987). To characterize the mechanism responsible for this increase, the effect of vitamin D3 depletion on key physical and morphological properties of cardiac muscle was examined. Depletion of vitamin D3 increased the heart weight/body weight ratio. This increase could neither be blocked by limiting hypocalcemia nor reversed by restoring increasing serum calcium levels. The cardiomegaly observed 9 wk after vitamin D3 depletion was not accompanied by an increase in myocardial water content or leakage of myocardial creatine phosphokinase and was not caused by myocardial cell hypertrophy. Histological examination of ventricular muscle from vitamin D3-deficient rats revealed a significant decrease in myofibrillar area and a significant increase in extracellular space. The increase in extracellular space was accompanied by a significant increase in myocardial collagen. Prevention of hypocalcemia in the vitamin D3-deficient rats did not prevent the increase in myocardial collagen. Such alterations in the physical and morphological properties of myocardial tissue might represent the basis for the change in myocardial contractile function that accompanies lengthy periods of vitamin D3 deficiency.

https://pubmed.ncbi.nlm.nih.gov/2154115/

"Depletion of vitamin D3 increased the heart weight/body weight ratio. This increase could neither be blocked by limiting hypocalcemia nor reversed by restoring increasing serum calcium levels."

Kidney Blood Press Res
Epub 2014 Sep 19

Maternal vitamin D deficiency and fetal programming-- lessons learned from humans and mice

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PMID: 25300533 DOI: 10.1159/000355809

Background/aims: Cardiovascular disease partially originates from poor environmental and nutritional conditions in early life. Lack of micronutrients like 25 hydroxy vitamin D3 (25OHD) during pregnancy may be an important treatable causal factor. The present study explored the effect of maternal 25OHD deficiency on the offspring.
Methods: We performed a prospective observational study analyzing the association of maternal 25OHD deficiency during pregnancy with birth outcomes considering confounding. To show that vitamin D deficiency may be causally involved in the observed associations, mice were set on either 25OHD sufficient or insufficient diets before and during pregnancy. Growth, glucose tolerance and mortality was analyzed in the F1 generation.
Results: The clinical study showed that severe 25OHD deficiency was associated with low birth weight and low gestational age. ANCOVA models indicated that established confounding factors such as offspring sex, smoking during pregnancy and maternal BMI did not influence the impact of 25OHD on birth weight. However, there was a significant interaction between 25OHD and gestational age. Maternal 25OHD deficiency was also independently associated with low APGAR scores 5 minutes postpartum. The offspring of 25OHD deficient mice grew slower after birth, had an impaired glucose tolerance shortly after birth and an increased mortality during follow-up.
Conclusions: Our study demonstrates an association between maternal 25OHD and offspring birth weight. The effect of 25OHD on birth weight seems to be mediated by vitamin D controlling gestational age. Results from an animal experiment suggest that gestational 25OHD insufficiency is causally linked to adverse pregnancy outcomes. Since birth weight and prematurity are associated with an adverse cardiovascular outcome in later life, this study emphasizes the need for novel monitoring and treatment guidelines of vitamin D deficiency during pregnancy.

https://pubmed.ncbi.nlm.nih.gov/25300533/

"Cardiovascular disease partially originates from poor environmental and nutritional conditions in early life. Lack of micronutrients like 25 hydroxy vitamin D3 (25OHD) during pregnancy may be an important treatable causal factor. Results from an animal experiment suggest that gestational 25OHD insufficiency is causally linked to adverse pregnancy outcomes."

Observational Study Medicina (Kaunas)
October 2021

Effects of Supplementation in Vitamin D3 Deficient or Insufficient Children with Allergic Diseases

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PMID: 34684089 PMCID: PMC8538765 DOI: 10.3390/medicina57101052

Background and Objectives: Although vitamin D insufficiency or deficiency is prevalent in children with allergic diseases, recommendations for supplementation dosing regimens are imprecise and variable in the literature, because clinical trials aiming to determine optimal doses were scarce in the past. This study aimed to investigate supplementation of vitamin D3 that may achieve therapeutically effective but not toxic serum levels in a subpopulation of children with allergic diseases and concomitant hypovitaminosis D. Materials and ***Methods***: The retrospective, observational study with a cross-sectional design included 94 children suffering from allergic diseases and having vitamin D deficiency/insufficiency who were prescribed high-dose vitamin D3 supplementation by a pediatrician for at least 6 weeks and not more than 9 weeks. Serum levels of the major metabolite of vitamin D (25-(OH)D) were determined in all children twice: before and two weeks after the end of vitamin D3 supplementation.
Results: An increase in serum level of the 25-(OH)D after supplementation was significant. However, if the subjects had higher serum levels of the 25-(OH)D before the supplementation, and if the supplementation lasted 8 instead of 6 weeks, the absolute increase in serum level of the 25-(OH)D was lower. Patients taking corticosteroids as inhalation or intranasally had a more intense effect of vitamin D3 supplementation, i.e., the absolute increase in levels of 25-(OH)D was higher than in patients not using such medication.
Conclusions: Vitamin D deficiency and insufficiency in children with allergic diseases can be treated with maximal recommended doses of vitamin D3 for a short period of time, especially if they were prescribed with inhalation or intranasal corticosteroids.

https://pubmed.ncbi.nlm.nih.gov/34684089/

"Vitamin D deficiency and insufficiency in children with allergic diseases can be treated with maximal recommended doses of vitamin D3 for a short period of time, especially if they were prescribed with inhalation or intranasal corticosteroids."

Ital J Pediatr
January 2019

Effect of vitamin D3 seasonal supplementation with 1500 IU/day in north Italian children (DINOS study)

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PMID: 30691521 PMCID: PMC6350345 DOI: 10.1186/s13052-018-0590-x

Background: The appropriate dose of vitamin D supplementation in children is still debated. We calculated that the recommended dose of 600-1000 IU vitamin D3/day is not sufficient to reach a serum 25-hydroxyvitamin D (25-OH-D) level of at least 30 ng/ml (75 nmol/l) in north Italian children > 12 months. The aim of this study was to analyse the effect of seasonal supplementation with 1500 IU (=37.5 µg) vitamin D3/day.
Methods: DINOS (D-vitamIN Oral Supplementation) study was a pilot, monocentric, non-random case-control register study. It was conducted in a paediatric primary care setting near Padova (North Italy, 45°N latitude). The data of 203 children (girls:boys 1:1,33) aged 2-15 years, collected between November 2010 and January 2015, were analysed. Active group A (n = 82) were given 1500 IU vitamin D3/day from November to April; control Group B (n = 121) received no supplementation. The serum 25-OH-D test was part of a laboratory tests panel and performed using a chemiluminescence immunoassay method.
Results: Serum 25-OH-D mean level + standard deviation throughout the period was 32 + 13 ng/ml (80 + 32 nmol/l) in group A vs 22 + 10 ng/ml (55 + 25 nmol/l) in group B. In group A 12% had vitamin D deficiency 25-OH-D < 20 ng/ml (50 nmol/l) and 1.2% severe vitamin D deficiency 25-OH-D < 10 ng/ml (25 nmol/l). In group B 46% had vitamin D deficiency and 9% severe deficiency (P < 0.001). In group A mean levels were normal or near-normal all the year except in May. Group B reached mean 25-OH-D levels close to 30 ng/ml (75 nmol/l) only in late summer. The active group mean 25-OH-D level was normal in preschoolers and schoolers but not in adolescents. Non-white children had a three-times vitamin D deficiency probability despite supplementation.
Conclusions: Vitamin D supplementation with at least 1500 IU vitamin D3/day from November to April was found appropriate for children in North Italy. A prolongation until May could be useful. Higher doses and/or prolonged periods could be more appropriate especially in adolescents and in non-white children.

https://pubmed.ncbi.nlm.nih.gov/30691521/

"Vitamin D supplementation with at least 1500 IU vitamin D3/day from November to April was found appropriate for children in North Italy. A prolongation until May could be useful. Higher doses and/or prolonged periods could be more appropriate especially in adolescents and in non-white children."

REVIEW Open Access

The importance of vitamin d metabolism as a potential prophylactic, immunoregulatory and neuroprotective treatment for COVID-19

Review J Transl Med
August 2020

The importance of vitamin d metabolism as a potential prophylactic, immunoregulatory and neuroprotective treatment for COVID-19

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PMID: 32847594 PMCID: PMC7447609 DOI: 10.1186/s12967-020-02488-5

The coronavirus disease 2019 (COVID-19) pandemic has led to a declaration of a Public Health Emergency of International Concern by the World Health Organization. As of May 18, 2020, there have been more than 4.7 million cases and over 316,000 deaths worldwide. COVID-19 is caused by a highly infectious novel coronavirus known as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), leading to an acute infectious disease with mild-to-severe clinical symptoms such as flu-like symptoms, fever, headache, dry cough, muscle pain, loss of smell and taste, increased shortness of breath, bilateral viral pneumonia, conjunctivitis, acute respiratory distress syndromes, respiratory failure, cytokine release syndrome (CRS), sepsis, etc. While physicians and scientists have yet to discover a treatment, it is imperative that we urgently address 2 questions: how to prevent infection in immunologically naive individuals and how to treat severe symptoms such as CRS, acute respiratory failure, and the loss of somatosensation. Previous studies from the 1918 influenza pandemic have suggested vitamin D's non-classical role in reducing lethal pneumonia and case fatality rates. Recent clinical trials also reported that vitamin D supplementation can reduce incidence of acute respiratory infection and the severity of respiratory tract diseases in adults and children. According to our literature search, there are no similar findings of clinical trials that have been published as of July 1st, 2020, in relation to the supplementation of vitamin D in the potential prevention and treatment for COVID-19. In this review, we summarize the potential role of vitamin D extra-renal metabolism in the prevention and treatment of the SARS-CoV-2 infection, helping to bring us slightly closer to fulfilling that goal. We will focus on 3 major topics here: 1. Vitamin D might aid in preventing SARS-CoV-2 infection: Vitamin D: Overview of Renal and Extra-renal metabolism

Direct and indirect effects of vitamin D deficiency on cardiovascular system

Direct effects

↑ LVH and cardiac contraction
↑ Cellular and VSM proliferation
↑ Atherosclerotic plaque
↑ Vascular calcification
↓ Endothelial cell function
↑ Renin/ angiotensin system

Indirect effects

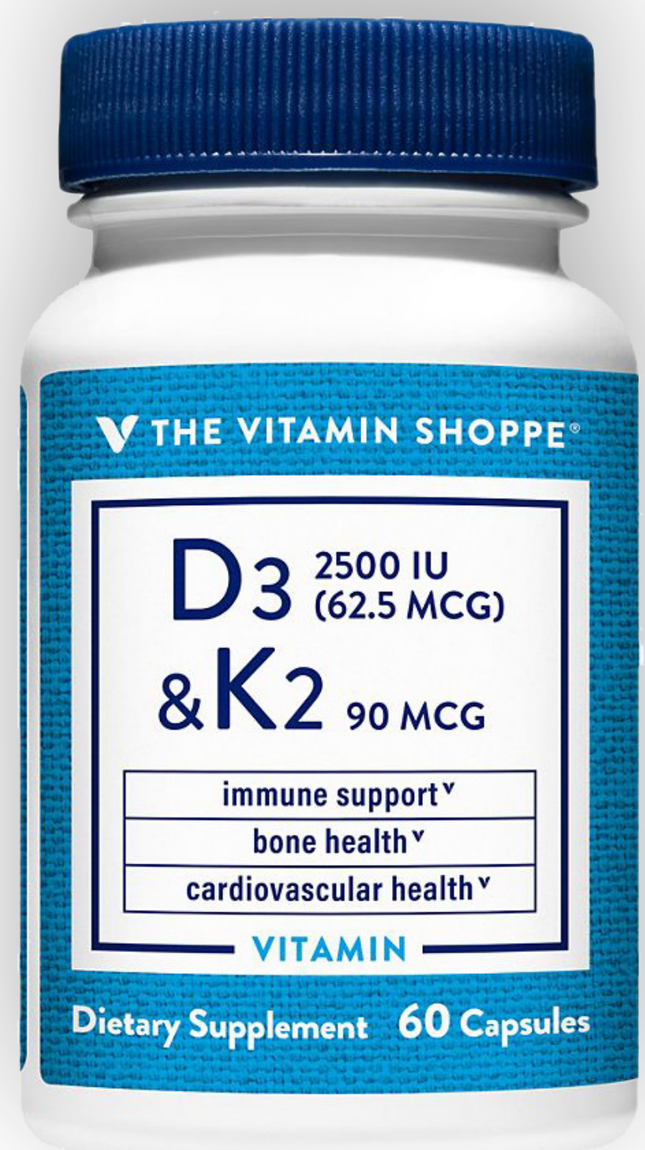
↑ Hypertension
↑ Diabetes
↑ Obesity
↑ Hyperlipidemia
↑ Insulin resistance
↓ HDL cholesterol
↑ Parathyroid hormone

and regulation. Vitamin D: Overview of molecular mechanism and multifaceted functions beyond skeletal homeostasis. Vitamin D: Overview of local immunomodulation in human infectious diseases. Anti-viral infection. Anti-malaria and anti-systemic lupus erythematosus (SLE). 2. Vitamin D might act as a strong immunosuppressant inhibiting cytokine release syndrome in COVID-19: Vitamin D: Suppression of key pro-inflammatory pathways including nuclear factor kappa B (NF-kB), interleukin-6 (IL-6), and tumor necrosis factor (TNF). 3. Vitamin D might prevent loss of neural sensation in COVID-19 by stimulating expression of neurotrophins like Nerve Growth Factor (NGF): Vitamin D: Induction of key neurotrophic factors.

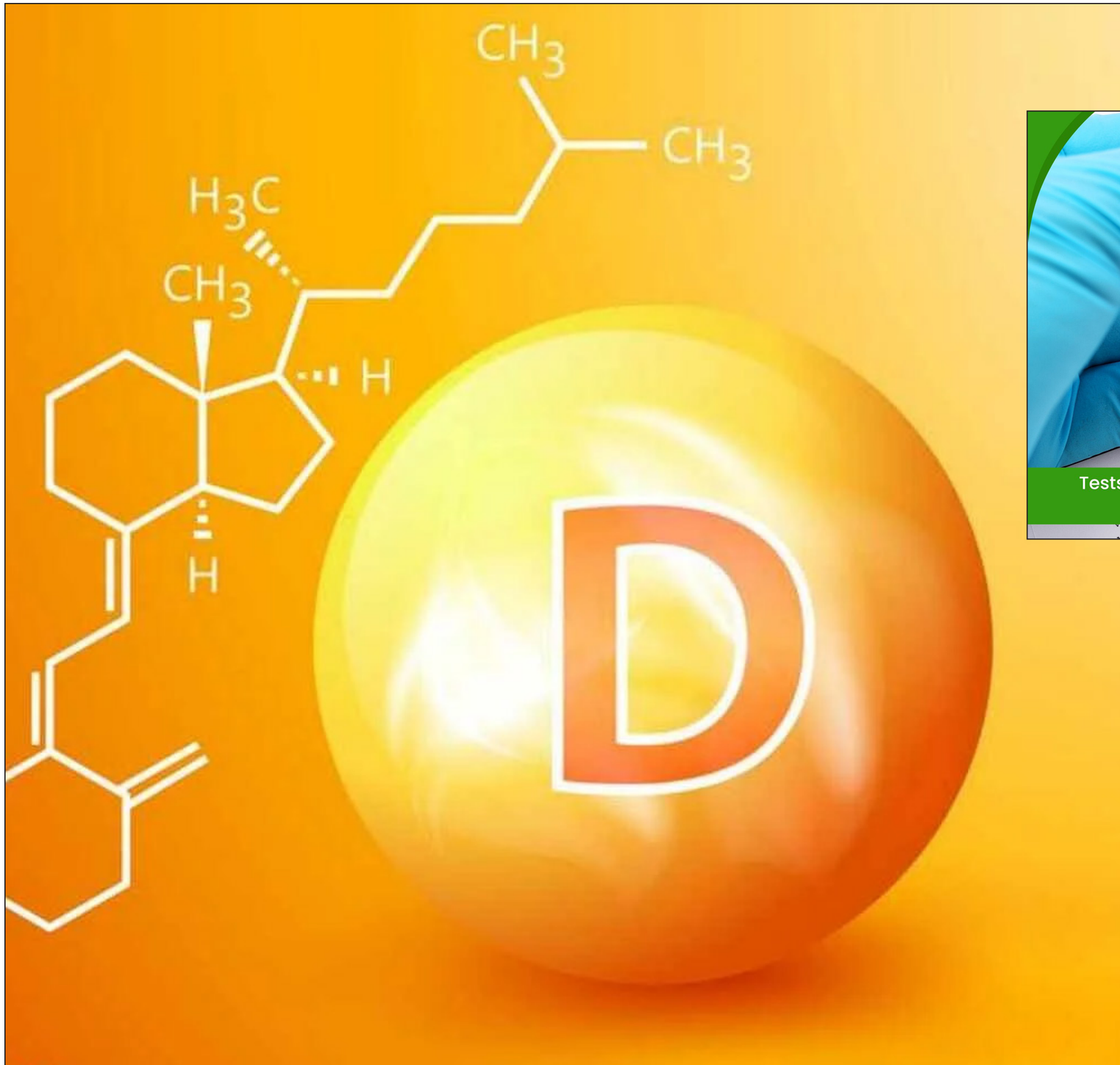
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7447609/pdf/12967_2020_Article_2488.pdf

"Previous studies from the 1918 influenza pandemic have suggested vitamin D's non-classical role in reducing lethal pneumonia and case fatality rates.

Recent clinical trials also reported that vitamin D supplementation can reduce incidence of acute respiratory infection and the severity of respiratory tract diseases in adults and children."



Use a 10,000 IU D3 with 90-93 micrograms of K2 and take with 400 milligrams of Magnesium daily



Tests are conducted to detect vitamin D deficiency and find cures if it has manifested in a person

Get Your

D3 Level

Checked

Every Year

ASCORBIC ACID · VITAMIN C
THE PEER REVIEW

Review Expert Rev Anti Infect Ther
Epub 2020 Aug 18

MATH+ Protocol for the Treatment of SARS-CoV-2 Infection: The Scientific Rationale

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PMID: 32809870 DOI: 10.1080/14787210.2020.1808462

Introduction: COVID-19 disease progresses through a number of distinct phases. The management of each phase is unique and specific. The pulmonary phase of COVID-19 is characterized by an organizing pneumonia with profound immune dysregulation, activation of clotting, and a severe microvascular injury culminating in severe hypoxemia. The core treatment strategy to manage the pulmonary phase includes the combination of methylprednisolone, ascorbic acid, thiamine, and heparin (MATH+ protocol). The rationale for the MATH+ protocol is reviewed in this paper.

Areas covered: We provide an overview on the pathophysiological changes occurring in patients with COVID-19 respiratory failure and a treatment strategy to reverse these changes thereby preventing progressive lung injury and death.

Expert opinion: While there is no single 'Silver Bullet' to cure COVID-19, we believe that the severely disturbed pathological processes leading to respiratory failure in patients with COVID-19 organizing pneumonia will respond to the combination of Methylprednisone, Ascorbic acid, Thiamine, and full anticoagulation with Heparin (MATH+ protocol).We believe that it is no longer ethically acceptable to limit management to 'supportive care' alone, in the face of effective, safe, and inexpensive medications that can effectively treat this disease and thereby reduce the risk of complications and death.

https://pubmed.ncbi.nlm.nih.gov/32809870/

FULL TEXT DOCUMENT:
https://www.tandfonline.com/doi/epub/10.1080/14787210.2020.1808462?needAccess=true

FLCCC MATH+ Protocol [English]:
https://covid19criticalcare.com/wp-content/uploads/2020/11/FLCCC-Alliance-I-MASKplus-Protocol-ENGLISH.pdf

FLCCC MATH+ Protocol [Spanish]:
https://covid19criticalcare.com/wp-content/uploads/2020/12/FLCCC_Alliance-I-MASKplus-Protocol-ESPANOL.pdf

FLCCC MATH+ Protocol [French]:
https://covid19criticalcare.com/wp-content/uploads/2020/12/FLCCC_Alliance-I-MASKplus-Protocol-FRANCAIS.pdf

FLCCC MATH+ Protocol [German]:
https://covid19criticalcare.com/wp-content/uploads/2020/12/FLCCC_Alliance-I-MASKplus-Protocol-DEUTSCH.pdf

Review Nutrients
December 2020

Vitamin C-An Adjunctive Therapy for Respiratory Infection, Sepsis and COVID-19

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PMID: 33297491 PMCID: PMC7762433 DOI: 10.3390/nu12123760

There are limited proven therapies for COVID-19. Vitamin C's antioxidant, anti-inflammatory and immunomodulating effects make it a potential therapeutic candidate, both for the prevention and amelioration of COVID-19 infection, and as an adjunctive therapy in the critical care of COVID-19. This literature review focuses on vitamin C deficiency in respiratory infections, including COVID-19, and the mechanisms of action in infectious disease, including support of the stress response, its role in preventing and treating colds and pneumonia, and its role in treating sepsis and COVID-19. The evidence to date indicates that oral vitamin C (2-8 g/day) may reduce the incidence and duration of respiratory infections and intravenous vitamin C (6-24 g/day) has been shown to reduce mortality, intensive care unit (ICU) and hospital stays, and time on mechanical ventilation for severe respiratory infections. Further trials are urgently warranted. Given the favourable safety profile and low cost of vitamin C, and the frequency of vitamin C deficiency in respiratory infections, it may be worthwhile testing patients' vitamin C status and treating them accordingly with intravenous administration within ICUs and oral administration in hospitalised persons with COVID-19.

https://pubmed.ncbi.nlm.nih.gov/33297491/

"C's antioxidant, anti-inflammatory and immunomodulating effects make it a potential therapeutic candidate, both for the prevention and amelioration of COVID-19 infection ... Given the favourable safety profile and low cost of vitamin C, and the frequency of vitamin C deficiency in respiratory infections, it may be worthwhile testing patients' vitamin C status and treating them accordingly with intravenous administration ..."

Review Molecules
November 2020

Mini-Review on the Roles of Vitamin C, Vitamin D, and Selenium i n the Immune System against COVID-19

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PMID: 33207753 PMCID: PMC7696052 DOI: 10.3390/molecules25225346

Low levels of micronutrients have been associated with adverse clinical outcomes during viral infections. Therefore, to maximize the nutritional defense against infections, a daily allowance of vitamins and trace elements for malnourished patients at risk of or diagnosed with coronavirus disease 2019 (COVID-19) may be beneficial. Recent studies on COVID-19 patients have shown that vitamin D and selenium deficiencies are evident in patients with acute respiratory tract infections. Vitamin D improves the physical barrier against viruses and stimulates the production of antimicrobial peptides. It may prevent cytokine storms by decreasing the production of inflammatory cytokines. Selenium enhances the function of cytotoxic effector cells. Furthermore, selenium is important for maintaining T cell maturation and functions, as well as for T cell-dependent antibody production. Vitamin C is considered an antiviral agent as it increases immunity. Administration of vitamin C increased the survival rate of COVID-19 patients by attenuating excessive activation of the immune response. Vitamin C increases antiviral cytokines and free radical formation, decreasing viral yield. It also attenuates excessive inflammatory responses and hyperactivation of immune cells. In this mini-review, the roles of vitamin C, vitamin D, and selenium in the immune system are discussed in relation to COVID-19.

https://pubmed.ncbi.nlm.nih.gov/33207753/

"Low levels of micronutrients have been associated with adverse clinical outcomes during viral infections. Administration of vitamin C increased the survival rate of COVID-19 patients by attenuating excessive activation of the immune response. Vitamin C increases antiviral cytokines and free radical formation, decreasing viral yield. It also attenuates excessive inflammatory responses and hyperactivation of immune cells."

Review Front Immunol
June 19, 2020

Quercetin and Vitamin C: An Experimental, Synergistic Therapy for the Prevention and Treatment of SARS-CoV-2 Related Disease (COVID-19)

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PMID: 32636851 PMCID: PMC7318306 DOI: 10.3389/fimmu.2020.01451

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) represents an emergent global threat which is straining worldwide healthcare capacity. As of May 27th, the disease caused by SARS-CoV-2 (COVID-19) has resulted in more than 340,000 deaths worldwide, with 100,000 deaths in the US alone. It is imperative to study and develop pharmacological treatments suitable for the prevention and treatment of COVID-19. Ascorbic acid is a crucial vitamin necessary for the correct functioning of the immune system. It plays a role in stress response and has shown promising results when administered to the critically ill. Quercetin is a well-known flavonoid whose antiviral properties have been investigated in numerous studies. There is evidence that vitamin C and quercetin co-administration exerts a synergistic antiviral action due to overlapping antiviral and immunomodulatory properties and the capacity of ascorbate to recycle quercetin, increasing its efficacy. Safe, cheap interventions which have a sound biological rationale should be prioritized for experimental use in the current context of a global health pandemic. We present the current evidence for the use of vitamin C and quercetin both for prophylaxis in high-risk populations and for the treatment of COVID-19 patients as an adjunct to promising pharmacological agents such as Remdesivir or convalescent plasma.

https://pubmed.ncbi.nlm.nih.gov/32636851/

"We present the current evidence for the use of vitamin C and quercetin both for prophylaxis in high-risk populations and for the treatment of COVID-19 patients ..."

Randomized Controlled Trial BMJ Open
July 8, 2020

Intravenous high-dose vitamin C for the treatment of severe COVID-19: study protocol for a multicentre randomised controlled trial

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PMID: 32641343 PMCID: PMC7348463 DOI: 10.1136/bmjopen-2020-039519

Introduction: The rapid worldwide spread of COVID-19 has caused a global health crisis. To date, symptomatic supportive care has been the most common treatment. It has been reported that the mechanism of COVID-19 is related to cytokine storms and subsequent immunogenic damage, especially damage to the endothelium and alveolar membrane. Vitamin C (VC), also known as L-ascorbic acid, has been shown to have antimicrobial and immunomodulatory properties. A high dose of intravenous VC (HIVC) was proven to block several key components of cytokine storms, and HIVC showed safety and varying degrees of efficacy in clinical trials conducted on patients with bacterial-induced sepsis and acute respiratory distress syndrome (ARDS). Therefore, we hypothesise that HIVC could be added to the treatment of ARDS and multiorgan dysfunction related to COVID-19.
Methods and analysis: The investigators designed a multicentre prospective randomised placebo-controlled trial that is planned to recruit 308 adults diagnosed with COVID-19 and transferred into the intensive care unit. Participants will randomly receive HIVC diluted in sterile water or placebo for 7 days once enrolled. Patients with a history of VC allergy, end-stage pulmonary disease, advanced malignancy or glucose-6-phosphate dehydrogenase deficiency will be excluded. The primary outcome is ventilation-free days within 28 observational days. This is one of the first clinical trials applying HIVC to treat COVID-19, and it will provide credible efficacy and safety data. We predict that HIVC could suppress cytokine storms caused by COVID-19, help improve pulmonary function and reduce the risk of ARDS of COVID-19.
Ethics and dissemination: The study protocol was approved by the Ethics Committee of Zhongnan Hospital of Wuhan University (identifiers: Clinical Ethical Approval No. 2020001). Findings of the trial will be disseminated through peer-reviewed journals and scientific conferences.

Trial registration number: NCT04264533.

https://pubmed.ncbi.nlm.nih.gov/32641343/

"Vitamin C (VC), also known as L-ascorbic acid, has been shown to have antimicrobial and immunomodulatory properties."

Review Front Immunol
October 28, 2020

The Long History of Vitamin C: From Prevention of the Common Cold to Potential Aid in the Treatment of COVID-19

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PMID: 33193359 PMCID: PMC7655735 DOI: 10.3389/fimmu.2020.574029

From Pauling's theories to the present, considerable understanding has been acquired of both the physiological role of vitamin C and of the impact of vitamin C supplementation on the health. Although it is well known that a balanced diet which satisfies the daily intake of vitamin C positively affects the immune system and reduces susceptibility to infections, available data do not support the theory that oral vitamin C supplements boost immunity. No current clinical recommendations support the possibility of significantly decreasing the risk of respiratory infections by using high-dose supplements of vitamin C in a well-nourished general population. Only in restricted subgroups (e.g., athletes or the military) and in subjects with a low plasma vitamin C concentration a supplementation may be justified. Furthermore, in categories at high risk of infection (i.e., the obese, diabetics, the elderly, etc.), a vitamin C supplementation can modulate inflammation, with potential positive effects on immune response to infections. The impact of an extra oral intake of vitamin C on the duration of a cold and the prevention or treatment of pneumonia is still questioned, while, based on critical illness studies, vitamin C infusion has recently been hypothesized as a treatment for COVID-19 hospitalized patients. In this review, we focused on the effects of vitamin C on immune function, summarizing the most relevant studies from the prevention and treatment of common respiratory diseases to the use of vitamin C in critical illness conditions, with the aim of clarifying its potential application during an acute SARS-CoV2 infection.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7655735/pdf/fimmu-11-574029.pdf

"In this review, we focused on the effects of vitamin C on immune function, summarizing the most relevant studies from the prevention and treatment of common respiratory diseases to the use of vitamin C in critical illness conditions, with the aim of clarifying its potential application during an acute SARS-CoV2 infection."

Review Pharmacol Rep
Epub 2020 Oct 28

Overview of the possible role of vitamin C in management of COVID-19

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PMID: 33113146 PMCID: PMC7592143 DOI: 10.1007/s43440-020-00176-1

The mainstay of management of coronavirus disease 2019 (COVID-19) is mainly supportive as to date there is no effective antiviral treatment, apart from remdesivir which has been approved by Food and Drug administration (FDA) for treatment of COVID-19, or vaccine. Supplementation with micronutrients, such as vitamins and minerals, has gained an increasing interest as part of the supportive management of COVID-19. Vitamin C levels in serum and leukocytes are depleted during the acute stage of infection owing to increased metabolic demands. High-dose vitamin C supplement helps to normalise both serum and leukocytes vitamin C levels. Vitamin C has multiple pharmacological characteristics, antiviral, anti-oxidant, anti-inflammatory and immunomodulatory effects, which make it a potential therapeutic option in management of COVID-19. The use of high dose of intravenous vitamin C for management of COVID-19 in China and the United Stated has shown promising results. There were no reported adverse reactions with the short-term use of high dose of vitamin C. Given the fact that vitamin C is cheap, available and safe drug with beneficial effects in management of viral infections and critically ill patients reported in previous clinical trials, it is sensible to add it to COVID-19 management protocol particularly if the current ongoing clinical trials testing the effect of vitamin C in management of COVID-19 show positive results.

https://pubmed.ncbi.nlm.nih.gov/33113146/

"Given the fact that vitamin C is cheap, available and safe drug with beneficial effects in management of viral infections and critically ill patients reported in previous clinical trials, it is sensible to add it to COVID-19 management protocol particularly if the current ongoing clinical trials testing the effect of vitamin C in management of COVID-19 show positive results."

Editorial Nutrients
October 27, 2020

The Emerging Role of Vitamin C in the Prevention and Treatment of COVID-19

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PMID: 33121019 PMCID: PMC7693980 DOI: 10.3390/nu12113286

Investigation into the role of vitamin C in the prevention and treatment of pneumonia and sepsis has been underway for many decades. This research has laid a strong foundation for translation of these findings into patients with severe coronavirus disease (COVID-19). Research has indicated that patients with pneumonia and sepsis have low vitamin C status and elevated oxidative stress. Administration of vitamin C to patients with pneumonia can decrease the severity and duration of the disease. Critically ill patients with sepsis require intravenous administration of gram amounts of the vitamin to normalize plasma levels, an intervention that some studies suggest reduces mortality. The vitamin has pleiotropic physiological functions, many of which are relevant to COVID-19. These include its antioxidant, anti-inflammatory, antithrombotic and immuno-modulatory functions. Preliminary observational studies indicate low vitamin C status in critically ill patients with COVID-19. There are currently a number of randomized controlled trials (RCTs) registered globally that are assessing intravenous vitamin C monotherapy in patients with COVID-19. Since hypovitaminosis C and deficiency are common in low-middle-income settings, and many of the risk factors for vitamin C deficiency overlap with COVID-19 risk factors, it is possible that trials carried out in populations with chronic hypovitaminosis C may show greater efficacy. This is particularly relevant for the global research effort since COVID-19 is disproportionately affecting low-middle-income countries and low-income groups globally. One small trial from China has finished early and the findings are currently under peer review. There was significantly decreased mortality in the more severely ill patients who received vitamin C intervention. The upcoming findings from the larger RCTs currently underway will provide more definitive evidence. Optimization of the intervention protocols in future trials, e.g., earlier and sustained administration, is warranted to potentially improve its efficacy. Due to the excellent safety profile, low cost, and potential for rapid upscaling of production, administration of vitamin C to patients with hypovitaminosis C and severe respiratory infections, e.g., COVID-19, appears warranted.

https://pubmed.ncbi.nlm.nih.gov/33121019/

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and potential for rapid upscaling of production,
administration of vitamin C to patients with
hypovitaminosis C and severe respiratory infections, e.g.,
COVID-19, appears warranted."

Nutrition
Epub 2020 Jul 25

Vitamin C as prophylaxis and adjunctive medical treatment for COVID-19?

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Severe acute respiratory syndrome coronavirus 2 causes the potentially fatal coronavirus disease 2019 (COVID-19). Already during the outbreak of the severe acute respiratory syndrome coronavirus 1, the use of vitamin C was suggested. Many patients with severe COVID-19 have elevated levels of the mediators interleukin-6 and endothelin-1. These mediators may explain the age dependence of COVID-19 pneumonia, the preponderance of male and obese or hypertensive patients, as well as of persons of color and smokers. There is clear evidence that vitamin C in high doses can reduce these mediators. Vitamin C is cheap and safe. Hence, using a relatively low dose of vitamin C as prophylaxis, and in cases of severe COVID-19, an (intravenous) high-dose regimen may be beneficial. Ongoing clinical trials are expected to provide more definitive evidence.

https://pubmed.ncbi.nlm.nih.gov/32911430/

"Vitamin C is cheap and safe.
Hence, using a relatively low dose
of vitamin C as prophylaxis,
and in cases of severe COVID-19,
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Journal List Crit Carev
Published online 2020 Apr 7
doi: 10.1186/s13054-020-02851-4
PMCID: PMC7137406
PMID: 32264963

A new clinical trial to test high-dose vitamin C in patients with COVID-19

Data Availability Statement

With the 2019 novel coronavirus (2019-nCoV) outbreak now spreading across the world, people are seeking ways in which to potentially protect themselves from the virus or to alleviate its effects once caught. One such means that is being touted online and in the media is vitamin C.

Vitamin C is best known for its antioxidant properties, being able to scavenge damaging reactive oxygen species, thus protecting the body's cells and tissues from oxidative damage and dysfunction. However, the vitamin also has numerous other important functions within the body, many of which are known to support healthy immune function. During infection, vitamin C levels can become depleted and a person's requirement for vitamin C increases with the severity of the infection [1]. In severe cases, this may require intravenous administration of gram doses in order to achieve high enough levels in the body to compensate for the enhanced turnover of the vitamin.

As of February 2020, the clinical characteristics of patients hospitalized with COVID-19-related pneumonia indicated that 26% were transferred to the ICU because of complications such as ARDS and shock [2]. A recently published RCT carried out in the USA in 167 patients with sepsis-related ARDS indicated that administration of ~ 15 g/day of IV vitamin C for 4 days may decrease mortality in these patients [3]. An earlier IV vitamin C trial of patients admitted to the ICU with pneumonia included hydrocortisone administration [4], however, systemic corticosteroid treatment has not been shown to have significant benefits in patients with COVID-19 [5].

Just recently registered on clincialtrials.gov (Identifier: NCT04264533), a new clinical trial to investigate vitamin C infusion for the treatment of severe 2019-nCoV infected pneumonia has begun in Wuhan, China. This is one of the first RCTs to test the effects of IV vitamin C in patients infected with this virus. In this trial, the investigators will treat 140 patients with a placebo control or intravenous vitamin C at a dose of 24 g/day for 7 days. They will assess requirements for mechanical ventilation and vasopressor drugs, organ failure scores, ICU length of stay and 28-day mortality.

The investigators of the new study hope to complete the trial by the end of September. Although the findings of this trial will be too late for the many thousands of people currently infected with the virus, the study will nevertheless provide valuable information as to the potential mitigation of symptoms by vitamin C during future viral outbreaks.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7137406/pdf/13054_2020_Article_2851.pdf

"Vitamin C is best known for its antioxidant properties, being able to scavenge damaging reactive oxygen species, thus protecting the body's cells and tissues from oxidative damage and dysfunction. However, the vitamin also has numerous other important functions within the body, many of which are known to support healthy immune function. During infection, vitamin C levels can become depleted and a person's requirement for vitamin C increases with the severity of the infection. In severe cases, this may require intravenous administration of gram doses in order to achieve high enough levels in the body to compensate for the enhanced turnover of the vitamin."

Expert Rev Anti Infect Ther
Epub 2020 Aug 1

The use of IV vitamin C for patients with COVID-19: a case series

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PMID: 32662690 PMCID: PMC7441798 DOI: 10.1080/14787210.2020.1794819

Background: The coronavirus disease 2019 (COVID-19) pandemic has affected almost 2.5 million people worldwide with almost 170,000 deaths reported to date. So far, there is scarce evidence for the current treatment options available for COVID-19. Vitamin C has previously been used for treatment of severe sepsis and septic shock. We reviewed the feasibility of using vitamin C in the setting of COVID-19 in a series of patients.
Methods: We sequentially identified a series of patients who were requiring at least 30% of FiO2 or more who received IV vitamin C as part of the COVID-19 treatment and analyzed their demographic and clinical characteristics. We compared inflammatory markers pre and post treatment including D-dimer and ferritin.
Results: We identified a total of 17 patients who received IV vitamin C for COVID-19. The inpatient mortality rate in this series was 12% with 17.6% rates of intubation and mechanical ventilation. We noted a significant decrease in inflammatory markers, including ferritin and D-dimer, and a trend to decreasing FiO2 requirements, after vitamin C administration.
Conclusion: The use of IV vitamin C in patients with moderate to severe COVID-19 disease may be feasible.

https://pubmed.ncbi.nlm.nih.gov/32662690/

"The use of IV vitamin C in patients with moderate to severe COVID-19 disease may be feasible."

Review Nutrients
April 2, 2020

Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths

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PMID: 32252338 PMCID: PMC7231123 DOI: 10.3390/nu12040988

The world is in the grip of the COVID-19 pandemic. Public health measures that can reduce the risk of infection and death in addition to quarantines are desperately needed. This article reviews the roles of vitamin D in reducing the risk of respiratory tract infections, knowledge about the epidemiology of influenza and COVID-19, and how vitamin D supplementation might be a useful measure to reduce risk. Through several mechanisms, vitamin D can reduce risk of infections. Those mechanisms include inducing cathelicidins and defensins that can lower viral replication rates and reducing concentrations of pro-inflammatory cytokines that produce the inflammation that injures the lining of the lungs, leading to pneumonia, as well as increasing concentrations of anti-inflammatory cytokines. Several observational studies and clinical trials reported that vitamin D supplementation reduced the risk of influenza, whereas others did not. Evidence supporting the role of vitamin D in reducing risk of COVID-19 includes that the outbreak occurred in winter, a time when 25-hydroxyvitamin D (25(OH)D) concentrations are lowest; that the number of cases in the Southern Hemisphere near the end of summer are low; that vitamin D deficiency has been found to contribute to acute respiratory distress syndrome; and that case-fatality rates increase with age and with chronic disease comorbidity, both of which are associated with lower 25(OH)D concentration. To reduce the risk of infection, it is recommended that people at risk of influenza and/or COVID-19 consider taking 10,000 IU/d of vitamin D3 for a few weeks to rapidly raise 25(OH)D concentrations, followed by 5000 IU/d. The goal should be to raise 25(OH)D concentrations above 40-60 ng/mL (100-150 nmol/L). For treatment of people who become infected with COVID-19, higher vitamin D3 doses might be useful. Randomized controlled trials and large population studies should be conducted to evaluate these recommendations.

https://pubmed.ncbi.nlm.nih.gov/32252338/

"The goal should be to raise 25(OH)D concentrations above 40-60 ng/mL (100-150 nmol/L). For treatment of people who become infected with COVID-19, higher vitamin D3 doses might be useful."

Journal ListInfect Chemother
Published online 2020 May 15
PMCID: PMC7335649
PMID: 32410417

Vitamin C as a Possible Therapy for COVID-19

Harri Hemiläcorresponding author1 and Elizabeth Chalker2
Author information Article notes Copyright and License information Disclaimer
See the article "Interim Guidelines on Antiviral Therapy for COVID-19" on page 281.
See the reply "Reply: Vitamin C as a Possible Therapy for COVID-19" in volume 52 on page 224.
This article has been cited by other articles in PMC.

Dear Editor,

Kim et al. reviewed potential therapeutic approaches against coronavirus diseases 2019 (COVID-19) [1]. We would like to propose that vitamin C should also be included as a possible treatment as it has numerous effects on the immune system [2,3].

In a meta-analysis of 29 controlled trials with 11,306 participants, we showed that regular vitamin C intake of around 1 g/day did not prevent upper respiratory tract infections (URTIs) [4]. However, the same trials found that vitamin C shortened and alleviated URTIs that occurred during the period of vitamin C administration. In adults the duration of infections was reduced by 8% and in children by 14% [4]. Given the low frequency and usually mild symptoms of URTIs, and the relatively small benefit, prophylactic daily vitamin C dosing does not seem worthwhile under normal circumstances. However, noting that many URTIs are caused by endemic coronaviruses, there is no reason or evidence to assume that vitamin C would be completely ineffective against COVID-19. Given that COVID-19 is often much more severe than ordinary URTIs, the above estimates might justify a regular increased daily intake of vitamin C while the prevalence of COVID-19 is high.

Furthermore, one of the major causes for concern with COVID-19 is the relatively high proportion of cases requiring intensive care unit (ICU) treatment. A meta-analysis of 12 trials with 1,766 patients in ICU found that vitamin C shortened ICU stay by 8% [5]. Another meta-analysis of eight trials found that vitamin C shortened the duration of mechanical ventilation in patients who required the longest ventilation [6]. There is evidence that vitamin C levels decline dramatically in critically ill patients [5,7]. Although 0.1 g/day of vitamin C can maintain a normal plasma level in a healthy person [8], much higher doses (1 – 4 g/day) are needed to increase plasma vitamin C levels of critically ill patients to within the normal range [5,9]. Vitamin C is a safe and inexpensive essential nutrient and therefore investigation of its possible effects on COVID-19 should be encouraged along with the several other potential treatments [1].

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7335649/pdf/ic-52-222.pdf

"Vitamin C is a safe and inexpensive essential nutrient and therefore investigation of its possible effects on COVID-19 should be encouraged along with the several other potential treatments."

Review Front Nutr
December 7, 2020

Zinc, Vitamin D and Vitamin C: Perspectives for COVID-19 With a Focus on Physical Tissue Barrier Integrity

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PMID: 33365326 PMCID: PMC7750357 DOI: 10.3389/fnut.2020.606398

Some nutrients play key roles in maintaining the integrity and function of the immune system, presenting synergistic actions in steps determinant for the immune response. Among these elements, zinc and vitamins C and D stand out for having immunomodulatory functions and for playing roles in preserving physical tissue barriers. Considering the COVID-19 pandemic, nutrients that can optimize the immune system to prevent or lower the risk of severe progression and prognosis of this viral infection become relevant. Thus, the present review aims to provide a comprehensive overview of the roles of zinc and vitamins C and D in the immune response to viral infections, focusing on the synergistic action of these nutrients in the maintenance of physical tissue barriers, such as the skin and mucous membranes. The evidence found in the literature shows that deficiency of one or more of these three elements compromises the immune response, making an individual more vulnerable to viral infections and to a worse disease prognosis. Thus, during the COVID-19 pandemic, the adequate intake of zinc and vitamins C and D may represent a promising pharmacological tool due to the high demand for these nutrients in the case of contact with the virus and onset of the inflammatory process. Ongoing clinical trials will help to clarify the role of these nutrients for COVID-19 management.

https://pubmed.ncbi.nlm.nih.gov/33365326/

"Some nutrients play key roles in maintaining the integrity and function of the immune system, presenting synergistic actions in steps determinant for the immune response. Among these elements, zinc and vitamins C and D stand out for having immunomodulatory functions and for playing roles in preserving physical tissue barriers."

Journal ListElsevier Public Health Emergency Collection
Published online 2020 Mar 26
doi: 10.1016/j.medidd.2020.100028
PMCID: PMC7167497
PMID: 32328576

Can early and high intravenous dose of vitamin C prevent and treat coronavirus disease 2019 (COVID-19)?

By Richard Z. Cheng

The COVID-19 (SARS-2-Cov) pandemic, first reported in Wuhan, China, is now spreading to many continents and countries, causing a severe public health burden. Currently, there is no vaccine or specific antiviral drug for this deadly disease. A quick, deployable and accessible, effective and safe treatment is urgently needed to save lives and curtail the spreading. Acute respiratory distress syndrome (ARDS) is a key factor of fatality. Significantly increased oxidative stress due to rapid release of free radicals and cytokines is the hallmark of ARDS which leads to cellular injury, organ failure and death. Early use of large dose antioxidants, such as vitamin C (VC) may become an effective treatment for these patients. Clinical studies also show that high-dose oral VC provides certain protection against viral infection. Neither intravenous nor oral administration of high-dose VC is associated with significant side effect. Therefore, this regimen should be included in the treatment of COVID-19 and used as a preventative measure for susceptible populations such as healthcare workers with higher exposure risks.

Coronaviruses and influenza are among the pandemic viruses that can cause lethal lung injuries and death from ARDS [[1], [2], [3]]. Viral infections could evoke "cytokine storm" that leads to lung capillary endothelial cell activation, neutrophil infiltration and increased oxidative stress (reactive oxygen and nitrogen species). ARDS, characteristic of severe hypoxemia, is usually accompanied by uncontrolled inflammation, oxidative injury and damage to the alveolar-capillary barrier [4]. Increased oxidative stress is a major insult in pulmonary injury including acute lung injury (ALI) and ARDS, two clinical manifestations of acute respiratory failure with substantially high morbidity and mortality [5,6].

In a report of 29 patients with COVID-19 pneumonia, 27 (93%) showed increased hsCRP, a marker of inflammation and oxidative stress [7]. Transcription factor, nuclear factor erythroid 2 (nfe2)-related factor 2 (nrf2), is a major regulator of antioxidant response element (ARE)-driven cytoprotective protein expression. Activation of Nrf2 signaling plays an essential role in preventing cells and tissues from injury induced by oxidative stress. VC, an important component of the cellular antioxidant system [8], is beneficial to critical care management [9]. Cytokine storm is observed in both viral and bacterial infections [3] and results in increased oxidative stress via a common and non-specific pathway. Since the prevention and management of oxidative stress could be realized by large dose of antioxidants, this approach may be applicable to COVID-19 with intravenous high-dose VC based on the outcome of three previous clinical studies involving a total of 146 patients with sepsis [10].

Hemila and colleagues reported that various high-dose intravenous VC infusions (e.g., 200 mg/kg body weight/day, divided into 4 doses) shortened the intensive care unit (ICU) stay by 7.8% [11], accompanied by a significant reduction in the mortality rate [12]. Such an experience was reproduced among patients ill with severe influenza [13,14]. Indeed, dietary antioxidants (VC and sulforaphane) were shown to decrease oxidative stress induced acute inflammatory lung injury in patients receiving mechanical ventilation [15]. In addition, oral VC (e.g., 6 g daily) was able to reduce viral infection risk [16] or to improve symptoms [17].

1 High-dose intravenous VC has also been successfully used in the treatment of 50 moderate to severe

COVID-19 patients in China. The doses used varied between 10 g and 20 g per day, given over a period of 8–10 h. Additional VC bolus may be required among patients in critical conditions. The oxygenation index was improving in real time and all the patients eventually cured and were discharged [18]. In fact, high-dose VC has been clinically used for several decades and a recent NIH expert panel document states clearly that this regimen (1.5 g/kg body weight) is safe and without major adverse events [19].

Because the development of efficacious vaccines and antiviral drugs takes time, VC and other antioxidants are among currently available agents to mitigate COVID-19 associated ARDS. Given the fact that high-dose VC is safe, healthcare professionals should take a close look at this opportunity. Obviously, well-designed clinical studies are absolutely needed to develop standard protocols for bedside use.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7167497/pdf/main.pdf

"Because the development of efficacious vaccines and antiviral drugs takes time, Vitamin C (VC) and other antioxidants are among currently available agents to mitigate COVID-19 associated ARDS. Given the fact that high-dose VC is safe, healthcare professionals should take a close look at this opportunity."

Review Maturitas
Epub 2020 Aug 9

Immune-boosting role of vitamins D, C, E, zinc, selenium and omega-3 fatty acids: Could they help against COVID-19?

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PMID: 33308613 PMCID: PMC7415215 DOI: 10.1016/j.maturitas.2020.08.003

The world is currently in the grips of the coronavirus disease (COVID-19) pandemic, caused by the SARS-CoV-2 virus, which has mutated to allow human-to-human spread. Infection can cause fever, dry cough, fatigue, severe pneumonia, respiratory distress syndrome and in some instances death. COVID-19 affects the immune system by producing a systemic inflammatory response, or cytokine release syndrome. Patients with COVID-19 have shown a high level of pro-inflammatory cytokines and chemokines. There are currently no effective anti-SARS-CoV-2 viral drugs or vaccines. COVID-19 disproportionately affects the elderly, both directly, and through a number of significant age-related comorbidities. Undoubtedly, nutrition is a key determinant of maintaining good health. Key dietary components such as vitamins C, D, E, zinc, selenium and the omega 3 fatty acids have well-established immunomodulatory effects, with benefits in infectious disease. Some of these nutrients have also been shown to have a potential role in the management of COVID-19. In this paper, evidence surrounding the role of these dietary components in immunity as well as their specific effect in COVID-19 patients are discussed. In addition, how supplementation of these nutrients may be used as therapeutic modalities potentially to decrease the morbidity and mortality rates of patients with COVID-19 is discussed.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7415215/pdf/main.pdf

"Undoubtedly, nutrition is a key determinant of maintaining good health. Key dietary components such as vitamins C, D, E, zinc, selenium and the omega 3 fatty acids have well-established immunomodulatory effects, with benefits in infectious disease. Some of these nutrients have also been shown to have a potential role in the management of COVID-19."

Review Infect Chemother
Epub 2020 Nov 24

Repositioning Vitamin C as a Promising Option to Alleviate Complications associated with COVID-19

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PMID: 33263242 PMCID: PMC7779993 DOI: 10.3947/ic.2020.52.4.461

Vitamin C, also known as L-ascorbic acid, is an essential vitamin with pleiotropic functions, ranging from antioxidant to anti-microbial functions. Evidence suggests that vitamin C acts against inflammation, oxidative stress, autophagy chaos, and immune dysfunction. The ability to activate and enhance the immune system makes this versatile vitamin a prospective therapeutic agent amid the current situation of coronavirus disease 2019 (COVID-19). Being highly effective against the influenza virus, causing the common cold, vitamin C may also function against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and its associated complications. Severe infections need higher doses of the vitamin to compensate for the augmented inflammatory response and metabolic demand that commonly occur during COVID-19. Compelling evidence also suggests that a high dose of vitamin C (1.5 g/kg body weight) in inflammatory conditions can result in effective clinical outcomes and thus can be employed to combat COVID-19. However, further studies are crucial to delineate the mechanism underlying the action of vitamin C against COVID-19. The current review aims to reposition vitamin C as an alternative approach for alleviating COVID-19-associated complications.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7779993/pdf/ic-52-461.pdf

"Vitamin C, also known as L-ascorbic acid, is an essential vitamin with pleiotropic functions, ranging from antioxidant to anti-microbial functions. Evidence suggests that vitamin C acts against inflammation, oxidative stress, autophagy chaos, and immune dysfunction."

Nutrients
August 2020

Could Vitamins Help in the Fight Against COVID-19?

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PMID: 32842513 PMCID: PMC7551685 DOI: 10.3390/nu12092550

There are limited proven therapeutic options for the prevention and treatment of COVID-19. The role of vitamin and mineral supplementation or "immunonutrition" has previously been explored in a number of clinical trials in intensive care settings, and there are several hypotheses to support their routine use. The aim of this narrative review was to investigate whether vitamin supplementation is beneficial in COVID-19. A systematic search strategy with a narrative literature summary was designed, using the Medline, EMBASE, Cochrane Trials Register, WHO International Clinical Trial Registry, and Nexis media databases. The immune-mediating, antioxidant and antimicrobial roles of vitamins A to E were explored and their potential role in the fight against COVID-19 was evaluated. The major topics extracted for narrative synthesis were physiological and immunological roles of each vitamin, their role in respiratory infections, acute respiratory distress syndrome (ARDS), and COVID-19. Vitamins A to E highlighted potentially beneficial roles in the fight against COVID-19 via antioxidant effects, immunomodulation, enhancing natural barriers, and local paracrine signaling. Level 1 and 2 evidence supports the use of thiamine, vitamin C, and vitamin D in COVID-like respiratory diseases, ARDS, and sepsis. Although there are currently no published clinical trials due to the novelty of SARS-CoV-2 infection, there is pathophysiologic rationale for exploring the use of vitamins in this global pandemic, supported by early anecdotal reports from international groups. The final outcomes of ongoing trials of vitamin supplementation are awaited with interest.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7551685/pdf/nutrients-12-02550.pdf

"Level 1 and 2 evidence supports the use of thiamine, vitamin C, and vitamin D in COVID-like respiratory diseases, ARDS, and sepsis."

Cureus
November 2020

The Role of Vitamin C as Adjuvant Therapy in COVID-19

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PMID: 33409026 PMCID: PMC7779177 DOI: 10.7759/cureus.11779

Background and objective: The anti-inflammatory properties of vitamin C (VC) and the promising results it has shown in the treatment for common cold have prompted clinicians to use it as adjuvant therapy in the treatment of COVID-19. The purpose of this study was to find out the role of VC as adjunctive therapy in coronavirus disease 2019 (COVID-19). Methodology This study was conducted from March to July 2020 in the COVID-19 unit of a tertiary care hospital in Karachi. In this randomized controlled trial (RCT), one group received the intervention [50 mg/kg/day of intravenous (IV) VC] along with the standard therapy, and the other group received standard therapy only. Data such as age, gender, vitals, and biochemical values as well as outcomes including the number of days required for treatment, hospital stay, need for ventilation, and mortality were compared between the two groups and recorded using a self-structured questionnaire.
Results: COVID-19 patients who received IV VC became symptom-free earlier (7.1 ± 1.8 vs. 9.6 ± 2.1 days, p-value: <0.0001) and spent fewer days in the hospital (8.1 ± 1.8 vs. 10.7 ± 2.2 days, p-value: <0.0001) compared to those who received standard therapy only. However, there was no significant difference in the need for mechanical ventilation (p-value: 0.406) and mortality (p-value: 0.31) between the two groups.
Conclusion: VC can significantly improve clinical symptoms in patients affected with COVID-19; however, it had no impact on mortality and the need for mechanical ventilation. More large-scale studies are required to further assess the role of VC in the treatment of COVID-19.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7779177/pdf/cureus-0012-00000011779.pdf

"Vitamin C can significantly improve clinical symptoms in patients affected with COVID-19."

Review Front Immunol
October 2020

Immune-Boosting, Antioxidant and Anti-inflammatory Food Supplements Targeting Pathogenesis of COVID-19

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PMID: 33117359 PMCID: PMC7575721 DOI: 10.3389/fimmu.2020.570122

The COVID-19 is an acute and contagious disease characterized by pneumonia and ARDS. The disease is caused by SARS-CoV-2, which belongs to the family of Coronaviridae along with MERS-CoV and SARS-CoV-1. The virus has the positive-sense RNA as its genome encoding for ~26 proteins that work together for the virus survival, replication, and spread in the host. The virus gets transmitted through the contact of aerosol droplets from infected persons. The pathogenesis of COVID-19 is highly complex and involves suppression of host anti-viral and innate immune response, induction of oxidative stress followed by hyper inflammation described as the "cytokine storm," causing the acute lung injury, tissue fibrosis, and pneumonia. Currently, several vaccines and drugs are being evaluated for their efficacy, safety, and for determination of doses for COVID-19 and this requires considerable time for their validation. Therefore, exploring the repurposing of natural compounds may provide alternatives against COVID-19. Several nutraceuticals have a proven ability of immune-boosting, antiviral, antioxidant, anti-inflammatory effects. These include Zn, vitamin D, vitamin C, curcumin, cinnamaldehyde, probiotics, selenium, lactoferrin, quercetin, etc. Grouping some of these phytonutrients in the right combination in the form of a food supplement may help to boost the immune system, prevent virus spread, preclude the disease progression to severe stage, and further suppress the hyper inflammation providing both prophylactic and therapeutic support against COVID-19.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7575721/pdf/fimmu-11-570122.pdf

"Several nutraceuticals have a proven ability of immune-boosting, antiviral, antioxidant, anti-inflammatory effects. These include Zn, vitamin D, vitamin C, curcumin, cinnamaldehyde, probiotics, selenium, lactoferrin, quercetin, etc. Grouping some of these phytonutrients in the right combination in the form of a food supplement may help to boost the immune system, prevent virus spread, preclude the disease progression to severe stage, and further suppress the hyper inflammation providing both prophylactic and therapeutic support against COVID-19."

Med Drug Discov
Epub 2020 Sep 18

Serum Levels of Vitamin C and Vitamin D in a Cohort of Critically Ill COVID-19 Patients of a North American Community Hospital Intensive Care Unit in May 2020: A Pilot Study

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PMID: 32964205 PMCID: PMC7499070 DOI: 10.1016/j.medidd.2020.100064

Background: The COVID-19 pandemic has placed an enormous and growing burden on the population and health infrastructure, warranting innovative ways to mitigate risk of contracting and developing severe forms of this disease. A growing body of literature raises the issue of vitamin C and vitamin D as a risk-assessment tool, and therapeutic option, in COVID-19.

Objective: The objective of this pilot study was to measure serum vitamin C and vitamin D levels in a cohort of patients with critical COVID-19 illness in our community hospital ICU, correlate with other illness risk factors (age, BMI, HgbA1c, smoking status), generate hypotheses, and suggest further therapeutic intervention studies.

Method: This pilot study included all 21 critically ill COVID-19 patients hospitalized in May 2020 in the ICU of North Suburban Medical Center, Thornton, Colorado, in whose care the principal investigator (C.A.) was involved. We measured patients' serum vitamin C and vitamin D levels, and standard risk factors like age, BMI, HbA1c, and smoking status. Variables in this study were gauged using descriptive statistics.

Results: Of 21 critically ill COVID-19 patients (15 males and 6 females, 17 Hispanic and 4 Caucasian, of median age 61 years, range 20-94), there were 11 survivors.Serum levels of vitamin C and vitamin D were low in most of our critically ill COVID-19 ICU patients.Older age and low vitamin C level appeared co-dependent risk factors for mortality from COVID-19 in our sample.Insulin resistance and obesity were prevalent in our small cohort, but smoking was not.

Conclusion: Our pilot study found low serum levels of vitamin C and vitamin D in most of our critically ill COVID-19 ICU patients. Older age and low vitamin C level appeared co-dependent risk factors for mortality. Many were also insulin-resistant or diabetic, overweight or obese, known as independent risk factors for low vitamin C and vitamin D levels, and for COVID-19. ***These findings suggest the need to further explore whether caring for COVID-19 patients ought to routinely include measuring and correcting serum vitamin C and vitamin D levels, and whether treating critically ill COVID-19 warrants acute parenteral vitamin C and vitamin D replacement.***

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7499070/pdf/main.pdf

Review Geriatr Nurs
Epub 2020 May 8

Vitamin C and Coronavirus

William Simonson 1

When deciding on a topic for this issue's column it seemed obvious to me to address some aspect of the elephant in the room… Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) or "COVID-19." There are so many aspects of the virus ….. which particular aspect of the topic should I address? Ultimately, the virus will only be fully-controlled when a safe and effective vaccine is available. Experts say that this will take at least 12–18 months, which is still record time for development of a vaccine. Perhaps it is wishful thinking on my part but I think such a vaccine might be available in less than one year. For what it is worth, I just heard an interview where the subject said that a vaccine may be available for first responders by this Autumn….let us hope so.

I have faith in the universities, private research laboratories and biotech companies working towards conquering this pandemic. It will be conquered and in-the-process the amazing leaps in knowledge that will come out of this will result in a much better understanding of viral infections which will help prevent a disaster like this from occurring again. In the meantime, as a stopgap measure, one or more therapeutic options may provide at least temporary control. To date there are no such proven options for prophylaxis or treatment but there are a rapidly growing number of possible therapies being discussed, researched and sometimes touted with little or no scientific rationale. Some of these potential therapies are old, perhaps repurposed pharmaceuticals, while some are high-tech, modern biologic agents that represent new approaches to control viral infections. For example, one proven approach for treating certain infectious diseases, including other coronaviruses, is the administration of convalescent plasma, collected from individuals who have recovered from an infection and are therefore able to make the appropriate antibodies which are then collected and given to those who have not yet been infected to provide them with passive immunity.1 It is hoped that this approach will be effective in treating coronavirus as it has been with other infectious diseases. Development of monoclonal antibodies specifically engineered to block the virus are another option as is the use of existing biologic products already indicated for conditions such as HIV and various cancers. It would be wonderful if one or more of these agents is able to block the virus to prevent infection or treat sick patients but one course of therapy from some of these biologicals may have a price tag of many thousands of dollars. This would add countless dollars to the global price tag that already amounts to trillions of dollars. Other possible therapies or adjuncts include zinc, chloroquine and hydroxychloroquine, the efficacy of which has not been proven and is less based on science than it is on "hunches and feelings" which is clearly not a scientific approach. Distressingly, to some people, the use of particular agents over others has become a partisan issue which I am having difficulty comprehending.

All this being said, I decided to focus on a product that has been proposed to prevent or treat COVID-19 and is indeed already used in clinical practice. After all, what's not to like about this popular vitamin, vitamin C? Most of the readers have a bottle of vitamin C tablets in their medicine cabinets. My Mom was a strong believer in the benefits of vitamin C and always encouraged me to take supplements or consume foods rich in the vitamin such as orange juice. Another reason for my selection of this topic is that vitamin C was made famous by Dr. Linus Pauling who graduated from the university where I am on faculty, Oregon State University. This institution houses the Linus Pauling institute.

Vitamin C has been studied for many years and we know that it is an important cofactor involved in the formation of blood vessels, cartilage, muscle and collagen in bone and is vital for the healing process. As an anti-oxidant, the vitamin might help protect cells from damage by chemical free radicals. It is thought that these chemicals contribute to heart disease, cancer and other diseases. Possible beneficial effects attributed to vitamin C include reducing endothelial dysfunction, managing hypertension, reducing cardiovascular disease

risk, and preventing stroke, certain types of cancer, diabetes, gout and possibly even Alzheimer's disease. The data on these possible uses is often controversial and/or conflicting and it is not entirely clear if benefits are at least partially the result of improved nutrition. Overall, regular use of vitamin C supplements shortens the duration of the common cold but does not reduce the risk of contracting a cold except in persons undergoing heavy physical stress (e.g. marathon runners, skiers, or soldiers in subarctic conditions) where the incidence of colds is cut in half. Taking vitamin C supplements once cold symptoms have already begun has no proven benefits.2 It is likely that this antiviral effect is why vitamin C has attracted interest as a possible treatment of COVID-19.

The recommended daily allowance for vitamin C intake is 90 mg. for adult men and 75 mg. for adult women with an additional daily 35 mg. for smokers of either gender.2 The Linus Pauling Institute recommends a daily vitamin C intake of at least 400 mg for adults >50 years. Dr. Pauling's dosing recommendation suggested that optimum daily intake may be about 2000 mg but he noted that the first 250 mg is most important for achieving satisfactory serum levels.3 Others recommend and are administering dosages that are much higher as discussed below. While anecdotal reports about the effects of medications are compelling, and provide what may appear to be convincing evidence that a particular medication or therapy possesses a specific therapeutic or negative effect, it is important not to get misled. It is important to re-emphasize that association does not mean causation. While anecdotal evidence is tempting to believe and may actually demonstrate an effect that is real, the proof of a drug's effect is only achieved through blinded, controlled studies published in peer-reviewed scientific journals. A recent scientific article published in 2019 before the detection of the novel coronavirus presents a meta-analysis of 18 controlled clinical trials with a total of more than 2000 patients looking at the effect of vitamin C on length of stay in the hospital intensive care unit and the duration of mechanical ventilation. Study results included the following: In 12 of the trials reviewed, length of ICU stay was reduced by 7.8% in patients receiving vitamin C. This was highly statistically significant. In six trials the length of ICU stay was reduced by 8.6% following oral administration of vitamin C in doses of 1–3 g/day. In three trials in which patients needed mechanical ventilation for over 24 h vitamin C shortened the duration of mechanical ventilation by 18.2%. All these data were highly statistically significant.4 This study did not include COVID-19 patients but the authors suggested that the effects of vitamin C on ICU patients should be investigated in more detail based on study results and what they refer to as the insignificant cost of vitamin C. It would be important to study this in patients with COVID-19 infection.

In a YouTube video interview, Ron Hunninghake, MD, medical director of the Riordan Clinic, a nutrition-based health facility in Kansas, stated that most doctors and medical schools are biased against nutritional medicine and that vitamin C is more likely to be adopted as a component of medical practice that could be referred to as nutritional, integrative, or wholistic medicine.5 Hunninghake refers the viewer to a recent study published in JAMA that showed that intravenous administration of 1.5 GM vitamin C every 6 hours significantly decreased mortality rate of septic patients with acute respiratory distress syndrome by 30%.6 Dr. Hunninghake reports administering intravenous vitamin C to 250,000 patients over his 31 years of practice and describes vitamin C as "The paramount rescue molecule in nature." His current protocol is to administer 7.5 g of vitamin C in 50 cc of fluid over 3–5 min and that patients tolerate this therapy very well including virtually no development of kidney stones. At least some hospital systems have adopted administration of vitamin C in patients infected with COVID-19. A NY newspaper reports that seriously sick patients in NY City's largest hospital system are being given vitamin C. A pulmonologist and critical care specialist Dr. Andrew G. Weber said that his intensive-care patients with the coronavirus immediately receive 1500 mg of vitamin C, administered intravenously, with that dose repeated three or four times a day. Dr. Weber stated, "The patients who received vitamin C did significantly better than those who did not get vitamin C." Since vitamin C levels in the body of coronavirus patients drops dramatically when sepsis develops, Dr. Weber adds "It makes all the sense in the world to try to maintain vitamin C levels in the body." Further comment from a spokesperson from Northwell which operates 23 NY hospitals stated that vitamin C was being "widely used" throughout the system with protocols varying according to the clinician's orders.7 To conclusively determine whether vitamin C therapy is beneficial

for treatment of COVID-19 a double-blind placebo-controlled study is needed. Indeed, such a study has been designed and recruitment of subjects began on February 14, 2020.8 Study design calls for intravenous administration of either 12 g of vitamin C or placebo to patients with severe pneumonia due to COVID-19 infection twice a day for 7 days. The study is projected to be completed by September 30, 2020 so, in the not-too-distant future, we should know whether this intensive high-dose vitamin C therapy is effective in treating COVID-19. Of course, question will still remain re: whether more frequent intravenous dosing is effective or whether oral vitamin C should be given as a preventive measure for COVID-19 infection and, if so, what dose should be used. Until then, individual consumers need to make their own decisions based on available data. As with all medications, a key component of this decision will be an analysis of potential risk v. potential benefit.

I know that I am going to follow Mom's advice and continue to take my vitamin C tablet every day.

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PMID: 32439200 PMCID: PMC7205675 DOI: 10.1016/j.gerinurse.2020.05.002

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7205675/pdf/main.pdf

Review Nutrients
May 2020

Strengthening the Immune System and Reducing Inflammation and Oxidative Stress through Diet and Nutrition: Considerations during the COVID-19 Crisis

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PMID: 32471251 PMCID: PMC7352291 DOI: 10.3390/nu12061562

The coronavirus-disease 2019 (COVID-19) was announced as a global pandemic by the World Health Organization. Challenges arise concerning how to optimally support the immune system in the general population, especially under self-confinement. An optimal immune response depends on an adequate diet and nutrition in order to keep infection at bay. For example, sufficient protein intake is crucial for optimal antibody production. Low micronutrient status, such as of vitamin A or zinc, has been associated with increased infection risk. Frequently, poor nutrient status is associated with inflammation and oxidative stress, which in turn can impact the immune system. Dietary constituents with especially high anti-inflammatory and antioxidant capacity include vitamin C, vitamin E, and phytochemicals such as carotenoids and polyphenols. Several of these can interact with transcription factors such as NF-kB and Nrf-2, related to anti-inflammatory and antioxidant effects, respectively. Vitamin D in particular may perturb viral cellular infection via interacting with cell entry receptors (angiotensin converting enzyme 2), ACE2. Dietary fiber, fermented by the gut microbiota into short-chain fatty acids, has also been shown to produce anti-inflammatory effects. In this review, we highlight the importance of an optimal status of relevant nutrients to effectively reduce inflammation and oxidative stress, thereby strengthening the immune system during the COVID-19 crisis.

https://pubmed.ncbi.nlm.nih.gov/32471251/

"In this review, we highlight the importance of an optimal status of relevant nutrients to effectively reduce inflammation and oxidative stress, thereby strengthening the immune system during the COVID-19 crisis."

Review Nutrients
May 2020

COVID-19: The Inflammation Link and the Role of Nutrition in Potential Mitigation

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PMID: 32438620 PMCID: PMC7284818 DOI: 10.3390/nu12051466

The novel coronavirus disease (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has engulfed the world, affecting more than 180 countries. As a result, there has been considerable economic distress globally and a significant loss of life. Sadly, the vulnerable and immunocompromised in our societies seem to be more susceptible to severe COVID-19 complications. Global public health bodies and governments have ignited strategies and issued advisories on various handwashing and hygiene guidelines, social distancing strategies, and, in the most extreme cases, some countries have adopted "stay in place" or lockdown protocols to prevent COVID-19 spread. Notably, there are several significant risk factors for severe COVID-19 infection. These include the presence of poor nutritional status and pre-existing noncommunicable diseases (NCDs) such as diabetes mellitus, chronic lung diseases, cardiovascular diseases (CVD), obesity, and various other diseases that render the patient immunocompromised. These diseases are characterized by systemic inflammation, which may be a common feature of these NCDs, affecting patient outcomes against COVID-19. In this review, we discuss some of the anti-inflammatory therapies that are currently under investigation intended to dampen the cytokine storm of severe COVID-19 infections. Furthermore, nutritional status and the role of diet and lifestyle is considered, as it is known to affect patient outcomes in other severe infections and may play a role in COVID-19 infection. This review speculates the importance of nutrition as a mitigation strategy to support immune function amid the COVID-19 pandemic, identifying food groups and key nutrients of importance that may affect the outcomes of respiratory infections.

https://pubmed.ncbi.nlm.nih.gov/32438620/

"This review speculates the importance of nutrition as a mitigation strategy to support immune function amid the COVID-19 pandemic, identifying food groups and key nutrients of importance that may affect the outcomes of respiratory infections."

Antioxidants (Basel)
Published online 2020 Dec 3
PMCID: PMC7761826
PMID: 33287462

Vitamin C and Cardiovascular Disease: An Update

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The potential beneficial effects of the antioxidant properties of vitamin C have been investigated in a number of pathological conditions. In this review, we assess both clinical and preclinical studies evaluating the role of vitamin C in cardiac and vascular disorders, including coronary heart disease, heart failure, hypertension, and cerebrovascular diseases. Pitfalls and controversies in investigations on vitamin C and cardiovascular disorders are also discussed.

1. Physiology of Vitamin C: Vitamin C is a carbohydrate-like substance first isolated in 1928 by Albert Szent-Györgyi from cabbage, paprika, and the adrenal glands of some animals [1,2]; it was later found to be identical with the antiscorbutic factor that had been isolated from lemon juice by Sylvester Solomon Zilva in 1924 [3]. Originally called 'hexuronic acid' by Györgyi, the current denomination as vitamin C was proposed in 1933 by Walter Norman Haworth [4,5].

Among the vastly biological functions in which vitamin C is involved, as a potent antioxidant and radical scavenger, it protects cell constituents against oxidative stress, mediated by reactive oxygen species (ROS) and free radicals [6,7,8]. Moreover, vitamin C redox potential allows the maintenance of reduced and regeneration of other antioxidants, including glutathione and α–tocopherol (vitamin E) [9,10,11]. It is also required for the synthesis of several crucial biomolecules since it acts as a cofactor of the monooxygenase and dioxygenase enzymes [12]. Vitamin C-dependent enzymatic reactions are involved in the biosynthesis of collagen and cellular procollagen secretion, L-carnitine, norepinephrine, epinephrine, and for the regulation of the biosynthesis of other molecules [13,14]. Furthermore, vitamin C intake from food or supplements can increase the bioavailability of iron by improving the absorption of the non-heme iron [15,16,17,18].

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7761826/pdf/antioxidants-09-01227.pdf

"Vitamin C-dependent enzymatic reactions are involved in the biosynthesis of collagen and cellular procollagen secretion, L-carnitine, norepinephrine, epinephrine, and for the regulation of the biosynthesis of other molecules."

Case Reports Am J Case Rep
July 2020

Unusual Early Recovery of a Critical COVID-19 Patient After Administration of Intravenous Vitamin C

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PMID: 32709838 PMCID: PMC7405920 DOI: 10.12659/AJCR.925521

BACKGROUND: Coronavirus disease 2019 (COVID-19) continues to spread, with confirmed cases now in more than 200 countries. Thus far there are no proven therapeutic options to treat COVID-19. We report a case of COVID-19 with acute respiratory distress syndrome who was treated with high-dose vitamin C infusion and was the first case to have early recovery from the disease at our institute. CASE REPORT: A 74-year-old woman with no recent sick contacts or travel history presented with fever, cough, and shortness of breath. Her vital signs were normal except for oxygen saturation of 87% and bilateral rhonchi on lung auscultation. Chest radiography revealed air space opacity in the right upper lobe, suspicious for pneumonia. A nasopharyngeal swab for severe acute respiratory syndrome coronavirus-2 came back positive while the patient was in the airborne-isolation unit. Laboratory data showed lymphopenia and elevated lactate dehydrogenase, ferritin, and interleukin-6. The patient was initially started on oral hydroxychloroquine and azithromycin. On day 6, she developed ARDS and septic shock, for which mechanical ventilation and pressor support were started, along with infusion of high-dose intravenous vitamin C. The patient improved clinically and was able to be taken off mechanical ventilation within 5 days. CONCLUSIONS:. Further studies will elaborate on the efficacy of intravenous vitamin C in critically ill COVID-19.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7405920/pdf/amjcaserep-21-e925521.pdf

"This report highlights the potential benefits of high-dose intravenous vitamin C in critically ill COVID-19 patients in terms of rapid recovery and shortened length of mechanical ventilation and ICU stay."

CLEVELAND CLINIC JOURNAL OF MEDICINE

COVID-19 Curbside Consults
What is the role of supplementation with ascorbic acid, zinc, vitamin D, or N-acetylcysteine for prevention or treatment of COVID-19?

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DOI: https://doi.org/10.3949/ccjm.87a.ccc046

Several agents intended to supplement dietary intake or endogenous molecules may have a theoretical role in preventing or treating COVID-19. Because of their potential to influence immune response, ascorbic acid (vitamin C), zinc, vitamin D, and N-acetylcysteine have been hypothesized to be useful for prevention or treatment of COVID-19. The authors outline the biologic plausibility, applicable clinical data, and potential role of each of these agents.

INTRODUCTION

As of yet, there is no high-quality evidence to support medication therapy for the prevention or treatment of patients with coronavirus disease 2019 (COVID-19). However, several agents intended to supplement dietary intake or endogenous molecules may have a theoretical role in preventing or treating the disease.

COVID-19 infection leads to upregulation of systemic inflammation as evidenced by elevated concentrations of pro-inflammatory cytokines interleukin 1 (IL-1), IL-6, and tumor necrosis factor (TNF) alpha, as well as higher concentrations of the anti-inflammatory cytokine IL-10. Additionally, patients with COVID-19 likely have evidence of oxidative stress, which is characterized by production of reactive oxygen species and reactive nitrogen species, and a concomitant deficiency of antioxidants. Reactive oxygen species and reactive nitrogen species are known to damage cellular biochemical pathways by causing DNA strand breaks, lipid peroxidation, and antioxidant and antiprotease degradation.1 There are multiple defense mechanisms against reactive oxygen species and nitrogen species, including enzymatic scavengers (superoxide dismutase, catalase, and glutathione peroxidase) and nonenzymatic molecules (glutathione and vitamins A, C, and E). It is the imbalance between production of reactive oxygen and nitrogen species and the antioxidant pool in the body that perpetuates further damage and, with a hyperinflammatory response, may contribute to severe manifestations of COVID-19. Because of their potential to influence immune response and reactive oxygen and nitrogen species, and because of their availability as over-the-counter medications, ascorbic acid (vitamin C), zinc, vitamin D, and N-acetylcysteine have been hypothesized to be useful for prevention or treatment of COVID-19. The biologic plausibility, applicable clinical data, and potential role of each of these agents are outlined below.

https://pubmed.ncbi.nlm.nih.gov/32513807/

Ann Palliat Med
Epub 2020 Nov 17

Beneficial aspects of high dose intravenous vitamin C on patients with COVID-19 pneumonia in severe condition: a retrospective case series study

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PMID: 33222462 DOI: 10.21037/apm-20-1387

Background: Coronavirus disease 2019 (COVID-19) is a global public health event without specific therapeutic agents till now. We aim to determine if high dose intravenous vitamin C (HDIVC) was effective for COVID-19 patients in severe condition.
Methods: COVID-19 patients admitted in Shanghai Public Health Clinical Center from January 22, 2020 to April 11, 2020 were retrospectively scrolled. The enrolled patients were those with confirmed diagnosis of severe or critical COVID-19 pneumonia, who received HDIVC within 24 hours after disease aggravation. Main clinical outcomes obtained from 3-5 days (day 3) and 7-10 days (day 7) after HDIVC were compared to the ones just before (day 0) HDIVC.
Results: Totally, twelve patients were enrolled including six severe [age of mean, 56; interquartile range (IQR), 32-65 years, 3 men] and six critical (age of mean, 63; IQR, 60-82 years, 4 men) patients. The dosage of vitamin C [median (IQR), mg/kg (body weight)/day] were [162.7 (71.1-328.6)] for severe and [178.6 (133.3-350.6)] for critical patients. By Generalized estimating equation (GEE) model, C-reactive protein (CRP) was found to decrease significantly from day 0 to 3 and 7 (severe: 59.01±37.9, 12.36±22.12, 8.95±20.4; critical: 92.5±41.21, 33.9±30.2, 59.56±41.4 mg/L). Lymphocyte and CD4+ T cell counts in severe patients reached to normal level since day 3. Similar improving trends were observed for PaO2/FiO2 (severe: 209.3±111.7, 313.4±146, 423.3±140.8; critical: 119.9±52.7, 201.8±86.64, 190.5±51.99) and sequential organ failure assessment score (severe: 2.83±1.72, 1.33±1.63, 0.67±1.03; critical: 6.67±2.34, 4.17±2.32, 3.83±2.56). Better improving effect was observed in severe than critical patients after HDIVC.
Conclusions: HDIVC might be beneficial in aspects of inflammatory response, immune and organ function for aggravation of COVID-19 patients. Further clinical trials are in warrant.

Trial registration: This trial has been retrospectively registered in Chinese Clinical Trail Registry (ChiCTR2000032716) on May 8, 2020. http://www.chictr.org.cn/showproj.aspx?proj=53389.

https://pubmed.ncbi.nlm.nih.gov/33222462/

"HDIVC might be beneficial in aspects of inflammatory response, immune and organ function for aggravation of COVID-19 patients.

Review Nutrients
April 1, 2021

Vitamin C in the Treatment of COVID-19

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PMID: 33916257 PMCID: PMC8065688 DOI: 10.3390/nu13041172

Vitamin C is an essential nutrient that serves as antioxidant and plays a major role as co-factor and modulator of various pathways of the immune system. Its therapeutic effect during infections has been a matter of debate, with conflicting results in studies of respiratory infections and in critically ill patients. This comprehensive review aimed to summarize the current evidence regarding the use of vitamin C in the prevention or treatment of patients with SARS-CoV2 infection, based on available publications between January 2020 and February 2021. Overall, 21 publications were included in this review, consisting of case-reports and case-series, observational studies, and some clinical trials. In many of the publications, data were incomplete, and in most clinical trials the results are still pending. No studies regarding prevention of COVID-19 with vitamin C supplementation were found. Although some clinical observations reported improved medical condition of patients with COVID-19 treated with vitamin C, available data from controlled studies are scarce and inconclusive. Based on the theoretical background presented in this article, and some preliminary encouraging studies, the role of vitamin C in the treatment of patients with SARS-CoV-2 infection should be further investigated.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8065688/pdf/nutrients-13-01172.pdf

"Vitamin C is an essential nutrient that serves as antioxidant and plays a major role as co-factor and modulator of various pathways of the immune system. Its therapeutic effect during infections ..."

Review Biomed Pharmacother
Epub 2020 Jul 3

Natural history of COVID-19 and current knowledge on treatment therapeutic options

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Despite intense research there is currently no effective vaccine available against the new severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) emerged in the later 2019 and responsible for the COVID-19 pandemic. This infectious and communicable disease has become one of the major public health challenges in the world. The clinical management of COVID-19 has been limited to infection prevention and control measures associated with supportive care such as supplemental oxygen and mechanical ventilation. Meanwhile efforts to find an effective treatment to inhibit virus replication, mitigate the symptoms, increase survival and decrease mortality rate are ongoing. Several classes of drugs, many of them already in use for other diseases, are being evaluated based on the body of clinical knowledge obtained from infected patients regarding to the natural history and evolution of the infection. Herein we will provide an updated overview of the natural history and current knowledge on drugs and therapeutic agents being tested for the prevention and treatment of COVID-19. These include different classes of drugs such as antiviral agents (chloroquine, ivermectin, nitazoxanide, hydroxychloroquine, lopinavir, remdesivir, tocilizumab), supporting agents (Vitamin C, Vitamin D, azithromycin, corticosteroids) and promising investigational vaccines. Considering the controversies and excessive number of compounds being tested and reported in the literature we hope that this review can provide useful and updated consolidated information on potential drugs used to prevent, control and treat COVID-19 patients worldwide.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7332915/pdf/main.pdf

"These include different classes of drugs such as antiviral agents (chloroquine, **ivermectin**, nitazoxanide, **hydroxychloroquine**, lopinavir, remdesivir, tocilizumab), supporting agents (**Vitamin C, Vitamin D, azithromycin, corticosteroids**) ..."

Review J Glob Antimicrob Resist
Epub 2020 Oct 13

Possible application of high-dose vitamin C in the prevention and therapy of coronavirus infection

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Coronaviruses such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and influenza viruses increase oxidative stress in the body leading to cellular and tissue damage. To combat this, administration of high-dose vitamin C (ascorbic acid or ascorbate), in addition to standard conventional supportive treatments, has been shown to be a safe and effective therapy for severe cases of respiratory viral infection. Morbidity, mortality, infectiveness and spread of infectious diseases are dependent on the host-pathogen relationship. Given the lack of effective and safe antiviral drugs for coronaviruses, there should be more attention in supporting host immune defence, cytoprotection and immunoregulation. Implementation of high-dose vitamin C therapy could dramatically reduce the need for high doses of corticosteroids, antibacterials and antiviral drugs that may be immunosuppressive, adrenal depressive and toxic, complicating the disease course. In order to effectively fight the novel SARS-CoV-2 virus, medical professionals should explore readily available pharmaceutical and nutritional therapeutic agents with proven antioxidant, anti-inflammatory and immunosupportive properties. Supplemental vitamin C may also provide additional benefits for the prevention of viral infections, shorten the disease course and lessen complications of the disease.

"Implementation of high-dose vitamin C therapy could dramatically reduce the need for high doses of corticosteroids, antibacterials and antiviral drugs that may be immunosuppressive, adrenal depressive and toxic, complicating the disease course."

Front Med (Lausanne)
January 2021

Vitamin C and COVID-19

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PMID: 33537320 PMCID: PMC7848027 DOI: 10.3389/fmed.2020.559811

In numerous animal studies, vitamin C has prevented and alleviated viral and bacterial infections. In a few dozen placebo-controlled trials with humans, vitamin C has shortened infections caused by respiratory viruses, which indicates that the vitamin can also influence viral infections in humans. In critically ill patients, plasma vitamin C levels are commonly very low. Gram doses of vitamin C are needed to increase the plasma vitamin C levels of critically ill patients to the levels of ordinary healthy people. A meta-analysis of 12 trials with 1,766 patients calculated that vitamin C reduced the length of ICU stay on average by 8%. Another meta-analysis found that vitamin C shortened the duration of mechanical ventilation in ICU patients. Two randomized placebo-controlled trials found statistically significant reduction in the mortality of sepsis patients. The effects of vitamin C on acute respiratory distress syndrome (ARDS) frequently complicating COVID-19 pneumonia should be considered. Vitamin C is a safe and inexpensive essential nutrient.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7848027/pdf/fmed-07-559811.pdf

"The effects of vitamin C on acute respiratory distress syndrome (ARDS) frequently complicating COVID-19 pneumonia should be considered.
Vitamin C is a safe and inexpensive essential nutrient."

Review J Transl Med
November 2020

COVID-19: Is there a role for immunonutrition in obese patient?

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On December 12, 2019 a new coronavirus (SARS-CoV-2) emerged in Wuhan, China, triggering a pandemic of severe acute respiratory syndrome in humans (COVID-19). Today, the scientific community is investing all the resources available to find any therapy and prevention strategies to defeat COVID-19. In this context, immunonutrition can play a pivotal role in improving immune responses against viral infections. Immunonutrition has been based on the concept that malnutrition impairs immune function. ***Therefore, immunonutrition involves feeding enriched with various pharmaconutrients (Omega 3 Fatty Acids, Vitamin C, Arginine, Glutamine, Selenium, Zinc, Vitamin, E and Vitamin D) to modulate inflammatory responses, acquired immune response and to improve patient outcomes. In literature, significant evidences indicate that obesity, a malnutrition state, negatively impacts on immune system functionality and on host defense, impairing protection from infections. Immunonutrients can promote patient recovery by inhibiting inflammatory responses and regulating immune function.*** Immune system dysfunction is considered to increase the risk of viral infections, such as SARS-CoV-2, and was observed in different pathological situations. Obese patients develop severe COVID-19 sequelae, due to the high concentrations of TNF-α, MCP-1 and IL-6 produced in the meantime by visceral and subcutaneous adipose tissue and by innate immunity. Moreover, leptin, released by adipose tissue, helps to increase inflammatory milieu with a dysregulation of the immune response. Additionally, gut microbiota plays a crucial role in the maturation, development and functions of both innate and adaptive immune system, as well as contributing to develop obese phenotype. The gut microbiota has been shown to affect lung health through a vital crosstalk between gut microbiota and lungs, called the "gut-lung axis". This axis communicates through a bi-directional pathway in which endotoxins, or microbial metabolites, may affect the lung through the blood and when inflammation occurs in the lung, this in turn can affect the gut microbiota. Therefore, the modulation of gut microbiota in obese COVID-19 patients can play a key role in immunonutrition therapeutic strategy. This umbrella review seeks to answer the question of whether a nutritional approach can be used to enhance the immune system's response to obesity in obese patients affected by COVID-19.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7647877/pdf/12967_2020_Article_2594.pdf

Review J Egypt Public Health Assoc
December 11, 2021

The protective role of vitamin C in the management of COVID-19: A Review

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PMID: 34894332 PMCID: PMC8665316 DOI: 10.1186/s42506-021-00095-w

Background: The outbreak of coronavirus infectious disease-2019 (COVID-19) is globally deemed a significant threat to human life. Researchers are searching for prevention strategies, mitigation interventions, and potential therapeutics that may reduce the infection's severity. One such means that is highly being talked in online and in social media is vitamin C.

Main text: Vitamin C is a robust antioxidant that boosts the immune system of the human body. It helps in normal neutrophil function, scavenging of oxidative species, regeneration of vitamin E, modulation of signaling pathways, activation of pro-inflammatory transcription factors, activation of the signaling cascade, regulation of inflammatory mediators, and phagocytosis and increases neutrophil motility to the site of infection. All of these immunological functions are required for the prevention of COVID-19 infection.

Conclusion: Considering the role of vitamin C, it would be imperative to administrate vitamin C for the management of severe COVID-19. However, there is no specific clinical data available to confirm the use of vitamin C in the current pandemic.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8665316/pdf/42506_2021_Article_95.pdf

"Considering the role of vitamin C, it would be imperative to administrate vitamin C for the management of severe COVID-19."

Review Life (Basel)
November 1, 2021

Vitamin C Intervention for Critical COVID-19: A Pragmatic Review of the Current Level of Evidence

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PMID: 34833042 PMCID: PMC8624950 DOI: 10.3390/life11111166

Severe respiratory infections are characterized by elevated inflammation and generation of reactive oxygen species (ROS) which may lead to a decrease in antioxidants such as vitamin C and a higher requirement for the vitamin. Administration of intravenous vitamin C to patients with pneumonia and sepsis appears to decrease the severity of the disease and potentially improve survival rate. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection causes pneumonia, sepsis and acute respiratory distress syndrome (ARDS) in severe cases, and is referred to as coronavirus disease 2019 (COVID-19). Patients with COVID-19 infection also appear to have depleted vitamin C status and require additional supplementation of vitamin C during the acute phase of the disease. To date there have been 12 vitamin C and COVID-19 trials published, including five randomised controlled trials (RCTs) and seven retrospective cohort studies. The current level of evidence from the RCTs suggests that intravenous vitamin C intervention may improve oxygenation parameters, reduce inflammatory markers, decrease days in hospital and reduce mortality, particularly in the more severely ill patients. High doses of oral vitamin C supplementation may also improve the rate of recovery in less severe cases. No adverse events have been reported in published vitamin C clinical trials in COVID-19 patients. Upcoming findings from larger RCTs will provide additional evidence on vitamin supplementation in COVID-19 patients.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8624950/pdf/life-11-01166.pdf

"The current level of evidence from the RCTs suggests that intravenous vitamin C intervention may improve oxygenation parameters, reduce inflammatory markers, decrease days in hospital and reduce mortality, particularly in the more severely ill patients. High doses of oral vitamin C supplementation may also improve the rate of recovery in less severe cases."

Review Life (Basel)
December 3, 2021

The Effects of Vitamin C on the Multiple Pathophysiological Stages of COVID-19

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Currently available anti-viral drugs may be useful in reducing the viral load but are not providing the necessary physiological effects to reduce the SARS-CoV-2 complications efficiently. Treatments that provide better clinical outcomes are urgently needed. Vitamin C (ascorbic acid, AA) is an essential nutrient with many biological roles that have been proven to play an important part in immune function; it serves as an antioxidant, an anti-viral, and exerts anti-thrombotic effects among many other physiological benefits. Research has proven that AA at pharmacological doses can be beneficial to patients with acute respiratory distress syndrome (ARDS) and other respiratory illnesses, including sepsis. In addition, High-Dose Intravenous Vitamin C (HDIVC) has proven to be effective in patients with different viral diseases, such as influenza, chikungunya, Zika, and dengue. Moreover, HDIVC has been demonstrated to be very safe. Regarding COVID-19, vitamin C can suppress the cytokine storm, reduce thrombotic complications, and diminish alveolar and vascular damage, among other benefits. Due to these reasons, the use of HDIVC should be seriously considered in complicated COVID-19 patients. In this article, we will emphasize vitamin C's multiple roles in the most prominent pathophysiological processes presented by the COVID-19 disease.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8708699/pdf/life-11-01341.pdf

"Regarding COVID-19,

vitamin C can suppress the cytokine storm,

reduce thrombotic complications, and diminish alveolar

and vascular damage, among other benefits."

LETTER Open Access

High-dose intravenous vitamin C may help in cytokine storm in severe SARS-CoV-2 infection

To the editor:

The complete mechanism of action of the SARS-CoV-2 remains unclear. The severity of the disease is probably linked to the "cytokine storm" that leads to the acute respiratory distress syndrome. Cytokine storm is an overwhelming increase of several inflammatory markers at once, and it is a cause of severity in some conditions such as sepsis, acute pancreatitis, and multiple sclerosis, among others.

These conditions, characterized by a variety of inflammatory etiologies, have the common prognostic of hemodynamic abnormalities, multiple organs failure, and high mortality rates. Treatment of cytokine storm associated syndromes usually focuses in this environment: intensive care of hemodynamic parameters, uphold of damaged organs, and supervision of coagulopathy. The main cause of the cytokine induction, however, must yet be treated and is the main reason why in bacterial sepsis antibiotics are used.

High doses of intravenous vitamin C, higher than 6 g per day (however, even 15 g/day, or more, are reported), have demonstrated efficacy in treatment of sepsis and acute pancreatitis [1, 2]. To the best of our knowledge, oral formulations cannot exert the same effects.

In parenteral administration of high doses, vitamin C may decrease several inflammatory parameters (cytokines, cellular response, and homeostatic control), already observed in human and animal models. As adverse effect, ascorbic acid may cause oxalate accumulation in the kidneys that can be prevented with the concomitant use of thiamine.

Recovery Trial [3] recently finished its dexamethasone arm in severe COVID-19 patients and has shown decrease in mortality among patients that requires mechanical ventilation and support of oxygen. We are convinced about a possible synergistic effect of vitamin C and this corticosteroid. Recently, Dr. Carr commented [4] about a new clinical trial in development in China, using intravenous vitamin C in high dose. This trial, registered by Dr. Peng (Wuhan University), is now closed, since new severe cases became rare in Wuhan. (Confirmed by Dr. Peng by e-mail, even if in clinicaltrials.gov the status of the trial is yet as "recruiting").

Dr. Hernández and colleagues proposed a protocol including vitamin C in high dose to be used in COVID-19 patients [5]. However, the manuscript is in Spanish, decreasing the accessibility of the information.

The protocol using intravenous high dosage of vitamin C, thiamine and a glucocorticoid (as dexamethasone) seems to be useful, not expensive, with low risk of severe adverse effects. The aim is providing further discussion about the recovery of complicated cases of cytokine storm associated to the SARS-CoV-2.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7424130/pdf/13054_2020_Article_3228.pdf

Review Diseases
June 28, 2021

The Potential Use of Vitamin C to Prevent Kidney Injury in Patients with COVID-19

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The newly found SARS-CoV-2 has led to the pandemic of COVID-19, which has caused respiratory distress syndrome and even death worldwide. This has become a global public health crisis. Unfortunately, elders and subjects with comorbidities have high mortality rates. One main feature of COVID-19 is the cytokine storm, which can cause damage in cells and tissues including the kidneys. Here, we reviewed the current literature on renal impairments in patients with COVID-19 and analyzed the possible etiology and mechanisms. In addition, we investigated the potential use of vitamin C for the prevention of renal injury in those patients. It appears that vitamin C could be helpful to improve the outcomes of patients with COVID-19. Lastly, we discussed the possible protective effects of vitamin C on renal functions in COVID-19 patients with existing kidney conditions.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8293113/pdf/diseases-09-00046.pdf

“ It appears that vitamin C could be helpful to improve the outcomes of patients with COVID-19. Lastly, we discussed the possible protective effects of vitamin C on renal functions in COVID-19 patients with existing kidney conditions.”

The Lancet Regional Health - Europe 11 (2021) 100272
The Lancet Regional Health - Europe
Available online 20 November 2021

The epidemiological relevance of the COVID-19-vaccinated population is increasing

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High COVID-19 vaccination rates were expected to reduce trans- mission of SARS-CoV-2 in populations by reducing the number of possible sources for transmission and thereby to reduce the burden of COVID-19 disease. Recent data, however, indicate that the epide- miological relevance of COVID-19 vaccinated individuals is increas- ing. In the UK it was described that secondary attack rates among household contacts exposed to fully vaccinated index cases was simi- lar to household contacts exposed to unvaccinated index cases (25% for vaccinated vs 23% for unvaccinated). 12 of 31 infections in fully vaccinated household contacts (39%) arose from fully vaccinated epi- demiologically linked index cases. Peak viral load did not differ by vaccination status or variant type [1]. In Germany, the rate of symp- tomatic COVID-19 cases among the fully vaccinated (“breakthrough infections”) is reported weekly since 21. July 2021 and was 16.9% at that time among patients of 60 years and older [2]. This proportion is increasing week by week and was 58.9% on 27. October 2021 (Figure 1) providing clear evidence of the increasing relevance of the fully vaccinated as a possible source of transmission. A similar situation was described for the UK. Between week 39 and 42, a total of 100.160 COVID-19 cases were reported among citizens of 60 years or older. 89.821 occurred among the fully vaccinated (89.7%), 3.395 among the unvaccinated (3.4%) [3]. One week before, the COVID-19 case rate per 100.000 was higher among the subgroup of the vaccinated compared to the subgroup of the unvaccinated in all age groups of 30 years or more. In Israel a nosocomial outbreak was reported involving 16 healthcare workers, 23 exposed patients and two family members. The source was a fully vaccinated COVID-19 patient. The vaccination rate was 96.2% among all exposed individu- als (151 healthcare workers and 97 patients). Fourteen fully vacci- nated patients became severely ill or died, the two unvaccinated patients developed mild disease [4]. The US Centres for Disease Con- trol and Prevention (CDC) identifies four of the top five counties with the highest percentage of fully vaccinated population (99.984.3%) as “high” transmission counties [5]. Many decisionmakers assume that the vaccinated can be excluded as a source of transmission. It appears to be grossly negligent to ignore the vaccinated population as a possible and relevant source of transmission when deciding about public health control measures. Figure 1 on following page.

Author Contribution statement
GK as the sole author of this Letter, contributed to all aspects of the text.
Declaration of Competing Interests statement
The author has no competing interests to declare

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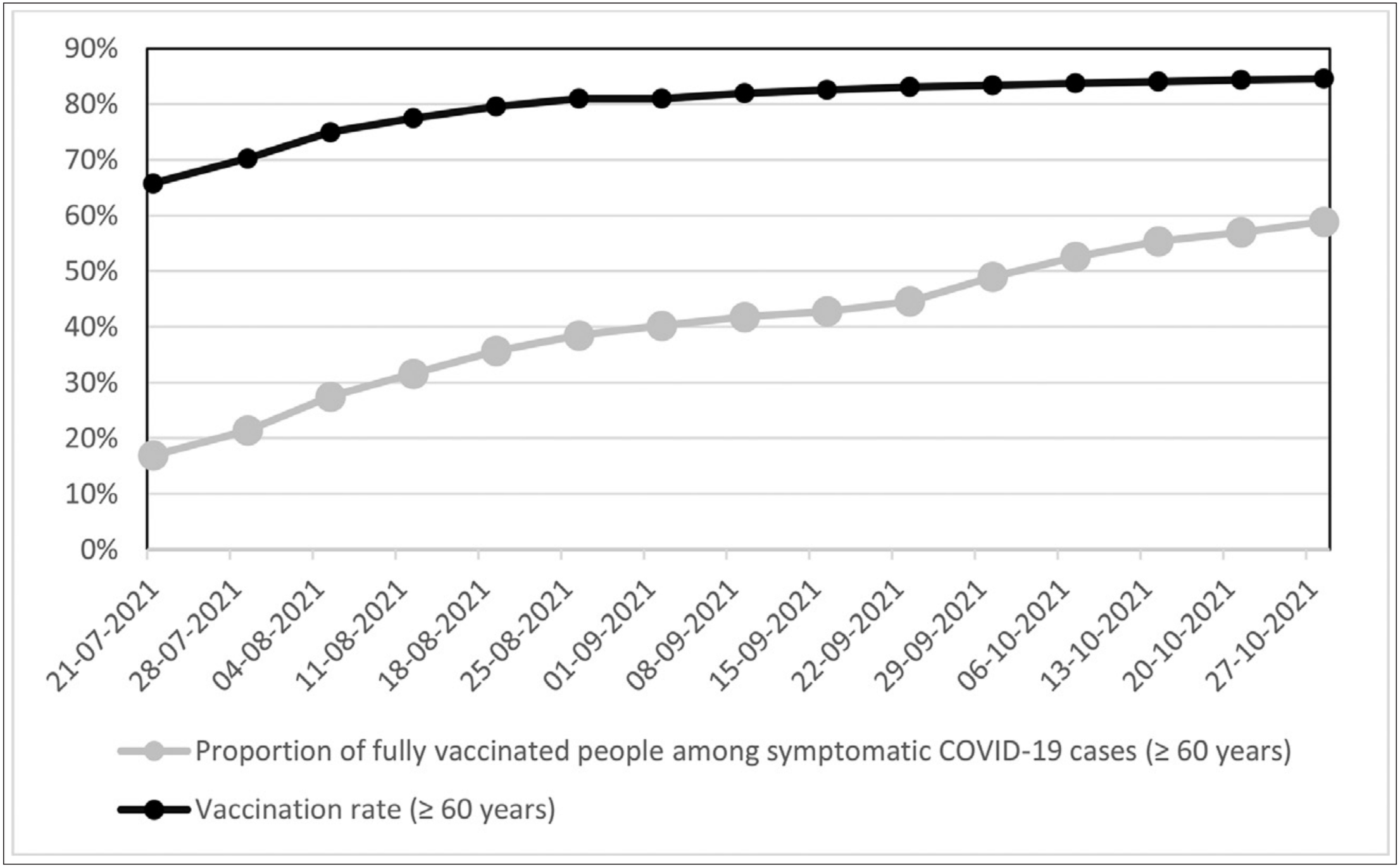

Figure 1. Vaccination rates and proportions of fully vaccinated people among symptomatic COVID-19 cases (! 60 years) in Germany between 21. July and 27. October 2021 based on the weekly reports from the Robert Koch-Institute [2].

On COVID vaccines: why they cannot work, and irrefutable evidence of their causative role in deaths after vaccination

Sucharit Bhakdi, MD and Arne Burkhardt, MD

This text is a written summary of Dr. Bhakdi's and Dr. Burkhardt's presentations at the Doctors for COVID Ethics symposium that was live-streamed by UKColumn on December 10th, 2021. The two presentations can be viewed at the very beginning of the video recording of the symposium.

The Authors

Dr. Bhakdi has spent his life practicing, teaching and researching medical microbiology and infectious diseases. He chaired the Institute of Medical Microbiology and Hygiene at the Johannes Gutenberg Unversity of Mainz, Germany, from 1990 until his retirement in 2012. He has published over 300 research articles in the fields of immunology, bacteriology, virology and parasitology, and served from 1990 to 2012 as Editor-in-Chief of Medical Microbiology and Immunology, one of the first scientific journals of this field that was founded by Robert Koch in 1887.

Dr. Arne Burkhardt is a pathologist who has taught at the Universities of Hamburg, Berne and Tübingen. He was invited for visiting professorships/study visits in Japan (Nihon University), the United States (Brookhaven National Institute), Korea, Sweden, Malaysia and Turkey. He headed the Institute of Pathology in Reutlingen for 18 years. Subsquently, he worked as an independent practicing pathologist with consulting contracts with laboratories in the US. Burkhardt has published more than 150 scientific articles in German and international scientific journals as well as contributions to handbooks in German, English and Japanese. Over many years he has audited and certified institutes of pathology in Germany.

The Evidence

We herewith present scientific evidence that calls for an immediate stop of the use of gene-based COVID-19 vaccines. We first lay out why the agents cannot protect against viral infection. While no positive effects can be expected, we show that the vaccines can trigger self-destructive processes that lead to debilitating illness and death.

Why the vaccines cannot protect against infection

A fundamental mistake underlying the development of the COVID-19 vaccines was to neglect the functional distinction between the two major categories of antibodies which the body produces in order to protect itself from pathogenic microbes.

The first category (secretory IgA) is produced by immune cells (lymphocytes) which are located directly underneath the mucous membranes that line the respiratory and intestinal tract. The antibodies produced by these lymphocytes are secreted through and to the surface of the mucous membranes.

These antibodies are thus on site to meet air-borne viruses, and they may be able to prevent viral binding and infection of the cells. The second category of antibodies (IgG and circulating IgA) occur in the bloodstream. These antibodies protect the internal organs of the body from infectious agents that try to spread via the bloodstream. Vaccines that are injected into the muscle – i.e., the interior of the body – will only induce IgG and circulating IgA, not secretory IgA. Such antibodies cannot and will not effectively protect the mucous membranes from infection by SARS-CoV-2. Thus, the currently observed "breakthrough infections" among

vaccinated individuals merely confirm the fundamental design flaws of the vaccines. Measurements of antibodies in the blood can never yield any information on the true status of immunity against infection of the respiratory tract. The inability of vaccine-induced antibodies to prevent coronavirus infections has been reported in recent scientific publications.

The vaccines can trigger self-destruction

A natural infection with SARS-CoV-2 (coronavirus) will in most individuals remain localized to the respiratory tract. In contrast, the vaccines cause cells deep inside our body to express the viral spike protein, which they were never meant to do by nature. Any cell which expresses this foreign antigen will come under attack by the immune system, which will involve both IgG antibodies and cytotoxic T- lymphocytes. This may occur in any organ. We are seeing now that the heart is affected in many young people, leading to myocarditis or even sudden cardiac arrest and death. How and why such tragedies might causally be linked to vaccination has remained a matter of conjecture because scientific evidence has been lacking. This situation has now been rectified.

Histopathologic studies: the patients

Histopathologic analyses have been performed on the organs of 15 persons who died after vaccination. The age, gender, vaccination record, and time of death after injection of each patient are listed in the table on the next page. The following points are of utmost importance:

• Prior to death, only 4 of the 15 patients had been treated in the ICU for more than 2 days. The majority were never hospitalized and died at home (5), on the street (1), at work (1), in the car (1), or in home-care facilities

• Therefore, in most cases, therapeutic intervention is unlikely to have significantly influenced the post-mortem findings.

• Not a single death was brought into any possible association with the vaccination by the coroner or the public prosecutor; this association was only established by our autopsy findings.

• The initially performed conventional post-mortems also uncovered no obvious hints to a possible role of vaccination, since the macroscopic appearance of the organs was overall unremarkable. In most cases, "rhythmogenic heart failure" was postulated as the cause of death. But our subsequent histopathological analyses then brought about a complete turnaround. A summary of the fundamental findings follows.

Histopathologic studies: findings

Histopathologic findings of a similar nature were detected in organs of 14 of the 15 deceased. Most frequently afflicted were the heart (14 of 15 cases) and the lung (13 of 15 cases). Pathologic alterations were furthermore observed in the liver (2 cases), thyroid gland (Hashimoto's thyroiditis, 2 cases), salivary glands (Sjögren`s Syndrome; 2 cases) and brain (2 cases).

A number of salient aspects dominated in all affected tissues of all cases:

1. inflammatory events in small blood vessels (endothelitis), characterized by an abundance of T- lymphocytes and sequestered, dead endothelial cells within the vessel lumen;

2. the extensive perivascular accumulation of T-lymphocytes;

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3. a massive lymphocytic infiltration of surrounding non-lymphatic organs or tissue with T- lymphocytes.

Lymphocytic infiltration occasionally occurred in combination with intense lymphocytic activation and follicle formation. Where these were present, they were usually accompanied by tissue destruction.

This combination of multifocal, T-lymphocyte-dominated pathology that clearly reflects the process of immunological self-attack is without precedent. Because vaccination was the single common denominator between all cases, there can be no doubt that it was the trigger of self-destruction in these deceased individuals.

Conclusion

Histopathologic analysis show clear evidence of vaccine-induced autoimmune-like pathology in multiple organs. That myriad adverse events deriving from such auto-attack processes must be expected to very frequently occur in all individuals, particularly following booster injections, is self- evident.

Beyond any doubt, injection of gene-based COVID-19 vaccines places lives under threat of illness and death. We note that both mRNA and vector-based vaccines are represented among these cases, as are all four major manufacturers.

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